

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty 30 micrograms/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial with a grey cap. Do not dilute prior to use.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty 30 micrograms/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older

Comirnaty is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 12 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Paediatric population

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Elderly population

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty 30 micrograms/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

Single dose vials

Single dose vials of Comirnaty contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

Comirnaty may be administered concomitantly with seasonal influenza vaccine.

Different injectable vaccines should be given at different injection sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of observational data from pregnant women vaccinated with Comirnaty during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Comirnaty can be used during pregnancy.

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to Comirnaty is negligible. Observational data from women who were breast-feeding after vaccination have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills ($> 30\%$), arthralgia ($> 20\%$), pyrexia and injection site swelling ($> 10\%$) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia ($> 30\%$), chills and arthralgia ($> 20\%$).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Participants 12 years of age and older – after subsequent booster doses

The safety of a booster dose of Comirnaty in participants 12 years of age and older is inferred from safety data from studies of a booster dose of Comirnaty in participants 18 years of age and older.

A subset of 325 adults 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 90 to 180 days after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of 1.4 months up to a data cut-off date of 11 March 2022. The most frequent adverse reactions in these participants were injection site pain ($> 70\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia and chills ($> 20\%$), and arthralgia ($> 10\%$).

In a subset from Study 4 (Phase 3), 305 adults > 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 5 to 12 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of at least 1.7 months up to a data cut-off date of 16 May 2022. The overall safety profile for the Comirnaty booster (fourth dose) was similar to that seen after the Comirnaty booster (third dose). The most frequent adverse reactions in participants > 55 years of age were injection site pain ($> 60\%$), fatigue ($> 40\%$), headache ($> 20\%$), myalgia and chills ($> 10\%$).

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified (see section 5.1).

Tabulated list of adverse reactions from clinical studies and post-authorisation experience in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty clinical trials and post-authorisation experience in individuals 12 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ^h |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Most cases appeared to be non-serious and temporary in nature.

Safety with concomitant vaccine administration

In Study 8, a Phase 3 study, participants 18 through 64 years of age who received Comirnaty coadministered with seasonal inactivated influenza vaccine (SIIV), quadrivalent followed 1 month later by placebo, were compared to participants who received an inactivated influenza vaccine with placebo followed 1 month later by Comirnaty alone (n= 553 to 564 participants in each group). Reactogenicity events were reported more frequently by participants who received Comirnaty coadministered with SIIV, quadrivalent, compared to participants who received Comirnaty alone, but overall the reactogenicity events were mostly mild to moderate in severity. The most common adverse reactions reported in the coadministration group and after Comirnaty alone were injection site pain (86.2% and 84.4%, respectively), fatigue (64.0% and 50.8%, respectively) and headache (47.2% and 37.8%, respectively).

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point

mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 2.

Table 2. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a = 18 325 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 3.

Table 3. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N ^a =20 998 Cases n1 ^b Surveillance time ^c (n2 ^d) | Placebo N ^a =21 096 Cases n1 ^b Surveillance time ^c (n2 ^d) | Vaccine efficacy % (95% CI ^e) |
|-------------------------------|--|--|--|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 4) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 4. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI^c) |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.

f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.

g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of

1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Immunogenicity in participants 18 years of age and older – after booster dose

Effectiveness of a booster dose of Comirnaty was based on an assessment of 50% neutralizing antibody titres (NT50) against SARS-CoV-2 (USA_WA1/2020) in Study 2. In this study, the booster dose was administered 5 to 8 months (median 7 months) after the second dose. In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4-fold rise in NT50 from baseline (before primary series). These analyses are summarized in Table 5.

Table 5. SARS-CoV-2 neutralization assay – NT50 (titre)[†] (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 through 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population[±]

| | n | 1 month after booster dose (95% CI) | 1 month after primary series (95% CI) | 1 month after booster dose - 1 month after primary series (97.5% CI) | Met noninferiority objective (Y/N) |
|---|------------------|--|---|--|------------------------------------|
| Geometric mean 50% neutralizing titre (GMT)^b | 212 ^a | 2 466.0 ^b (2 202.6, 2 760.8) | 755.7 ^b (663.1, 861.2) | 3.26 ^c (2.76, 3.86) | Y ^d |
| Seroresponse rate (%) for 50% neutralizing titre[†] | 200 ^e | 199 ^f 99.5% (97.2%, 100.0%) | 190 ^f 95.0% (91.0%, 97.6%) | 4.5% ^g (1.0%, 7.9% ^h) | Y ⁱ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

[†] SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of Comirnaty) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

[±] All eligible participants who had received 2 doses of Comirnaty as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Comirnaty, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an

appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

- n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
- Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80 .
- n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
- Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
- Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
- Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.

Relative vaccine efficacy in participants 16 years of age and older – after booster dose

An interim efficacy analysis of Study 4, a placebo-controlled booster study performed in approximately 10 000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up. The booster dose was administered 5 to 13 months (median 11 months) after the second dose. Vaccine efficacy of the Comirnaty booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed.

The relative vaccine efficacy information for participants 16 years of age and older without prior evidence of SARS-CoV-2 infection is presented in Table 6. Relative vaccine efficacy in participants with or without evidence of prior SARS-CoV-2 infection was 94.6% (95% confidence interval of 88.5% to 97.9%), similar to that seen in those participants without evidence of prior infection. Primary COVID-19 cases observed from 7 days after booster vaccination were 7 primary cases in the Comirnaty group, and 124 primary cases in the placebo group.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after booster vaccination – participants 16 years of age and older without evidence of infection – evaluable efficacy population

| First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|--|--|---|
| | Comirnaty N^a=4 695 Cases n1^b Surveillance Time^c (n2^d) | Placebo N^a=4 671 Cases n1^b Surveillance Time^c (n2^d) | Relative Vaccine Efficacy^e % (95% CI^f) |
| First COVID-19 occurrence from 7 days after booster vaccination | 6 0.823 (4 659) | 123 0.792 (4 614) | 95.3 (89.5, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.

- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non-booster).
- f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Immunogenicity of a booster dose following primary vaccination with another authorised COVID-19 vaccine

Effectiveness of a Comirnaty booster dose (30 mcg) in individuals who completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose) is inferred from immunogenicity data from an independent National Institutes of Health (NIH) study phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States. In this study, adults (range 19 to 80 years of age) who had completed primary vaccination with Moderna 100 mcg 2-dose series (N = 51, mean age 54±17), Janssen single dose (N = 53, mean age 48±14), or Comirnaty 30 mcg 2-dose series (N = 50, mean age 50±18) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection received a booster dose of Comirnaty (30 mcg). The boost with Comirnaty induced a 36, 12, and 20 GMR-fold rise in neutralising titres following the Janssen, Moderna, and Comirnaty primary doses, respectively.

Heterologous boosting with Comirnaty was also evaluated in the CoV-BOOST study (EudraCT 2021-002175-19), a multicentre, randomised, controlled, phase 2 trial of third dose booster vaccination against COVID-19, in which 107 adult participants (median age 71 years of age, interquartile range 54 to 77 years of age) were randomised at least 70 days post 2 doses of AstraZeneca COVID-19 Vaccine. After the AstraZeneca COVID-19 Vaccine primary series, pseudovirus (wild-type), neutralising antibody NT50 GMR-fold change increased 21.6-fold with heterologous Comirnaty booster (n = 95).

Immunogenicity in participants > 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)

In an interim analysis of a subset from Study 4 (Substudy E), 305 participants > 55 years of age who had completed a series of 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 5 to 12 months after receiving Dose 3. For the Immunogenicity subset data see Table 7.

Immunogenicity in participants 18 to ≤ 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 325 participants 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 90 to 180 days after receiving Dose 3. For the Immunogenicity subset data see Table 7.

Table 7. Summary of immunogenicity data from participants in C4591031 Substudy D (cohort 2 full expanded set) and Substudy E (expanded cohort immunogenicity subset) who received Comirnaty 30 mcg as booster (fourth dose) – participants without evidence of infection up to 1 month after booster dose – evaluable immunogenicity population

| | Dose/ sampling time point ^a | Substudy D (18 to ≤ 55 years of age) Comirnaty 30 mcg | | Substudy E (> 55 years of age) Comirnaty 30 mcg | |
|--|--|---|-------------------------------|---|-------------------------------|
| | | N ^b | GMT (95% CI ^d) | N ^b | GMT (95% CI ^d) |
| SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre) | 1/Prevax | 226 | 315.0 (269.0, 368.9) | 167 | 67.5 (52.9, 86.3) |
| | 1/1 Month | 228 | 1 063.2 (935.8, 1 207.9) | 163 | 455.8 (365.9, 567.6) |

| | | | | | |
|---|-----------|----------------------|---|----------------------|---|
| SARS-CoV-2 neutralization assay – reference strain – NT50 (titre) | 1/Prevax | 226 | 3 999.0 (3 529.5, 4 531.0) | 179 | 1 389.1 (1 142.1, 1 689.5) |
| | 1/1 Month | 227 | 12 009.9 (10 744.3, 13 424.6) | 182 | 5 998.1 (5 223.6, 6 887.4) |
| Seroresponse rate at 1 month post-Dose 4 | | N^c | n^e (%) (95% CI^f) | N^c | n^e (%) (95% CI^f) |
| SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre) | 1/1 Month | 226 | 91 (40.3%) (33.8, 47.0) | 149 | 85 (57.0%) (48.7, 65.1) |
| SARS-CoV-2 neutralization assay – reference strain – NT50 (titre) | 1/1 Month | 225 | 76 (33.8%) (27.6, 40.4) | 179 | 88 (49.2%) (41.6, 56.7) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Median time from Dose 3 to Dose 4 of Comirnaty 30 mcg is 4.0 months for Substudy D Cohort 2 and 6.3 months for Substudy E expanded cohort.

Note: Substudy D Full Expanded Set = Cohort 2 excluding the sentinel group; Substudy E Immunogenicity Subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving ≥ 4 -fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the post-vaccination measure of $\geq 4 \times$ LLOQ is considered a seroresponse.

- Protocol-specified timing for blood sample collection.
- N = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site

oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

2 years when stored at -90 °C to -60 °C.

Within the 2-year shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

Single dose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 2-year shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, within the 10-week storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Opened vials

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

Comirnaty dispersion is supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

Single dose vials pack size: 10 vials.

Multidose vials pack sizes: 10 vials or 195 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty 30 micrograms/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/013

Multidose vials

EU/1/20/1528/002

EU/1/20/1528/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty 10 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with an orange cap and must be diluted before use.

One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 10 micrograms of tozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty 10 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)

Comirnaty 10 micrograms/dose is administered intramuscularly after dilution as a single dose of 0.2 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Comirnaty 10 micrograms/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty 10 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty contain 10 doses of 0.2 mL of vaccine. In order to extract 10 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of observational data from pregnant women vaccinated with Comirnaty during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Comirnaty can be used during pregnancy.

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to Comirnaty is negligible. Observational data from women who were breast-feeding after vaccination have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of Comirnaty 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 50\%$), headache ($> 30\%$), injection site redness and swelling ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain ($> 60\%$), fatigue ($> 30\%$), headache ($> 20\%$), myalgia, chills, injection site redness and swelling ($> 10\%$).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills ($> 30\%$), arthralgia ($> 20\%$), pyrexia and injection site swelling ($> 10\%$) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia ($> 30\%$), chills and arthralgia ($> 20\%$).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Tabulated list of adverse reactions from clinical studies and post-authorisation experience in individuals 5 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty clinical trials and post-authorisation experience in individuals 5 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ⁱ |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 – 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 – 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring

significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 2.

Table 2. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n^{1b} Surveillance time^c (n2^d) | Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 3.

Table 3. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N^a=20 998 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=21 096 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI^e) |
|-------------------------------|---|---|--|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 4) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 4. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1 ^a Surveillance time (n2 ^b) | Placebo Cases n1 ^a Surveillance time (n2 ^b) | Vaccine efficacy % (95% CI ^c) |
|----------------------------------|--|---|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- n1 = Number of participants meeting the endpoint definition.

- b. n_2 = Number of participants at risk for the endpoint.
- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age ($n = 190$) to participants 16 to 25 years of age ($n = 170$).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 5. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 6.

Table 6. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 7.

Table 7. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| | Sampling time point ^a | | 1 month after booster dose/ 1 month after dose 2 |
|--|---|--|---|
| | 1 month after booster dose (n ^b =67) | 1 month after dose 2 (n ^b =96) | |
| Assay | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils)

consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

2 years when stored at -90 °C to -60 °C.

Within the 2-year shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 2-year shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, and within the 10-week storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1.3 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and an orange flip-off plastic cap with aluminium seal. Each vial contains 10 doses, see section 6.6.

Pack sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has an **orange plastic cap** and the product **name is Comirnaty 10 micrograms/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty for children aged 5 to 11 years.
Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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55131 Mainz
Germany
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Fax: +49 6131 9084-2121
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/004
EU/1/20/1528/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty 3 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with a maroon cap and must be diluted before use.

One vial (0.4 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 3 micrograms of tozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty 3 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in infants and children aged 6 months to 4 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Infants and children 6 months to 4 years of age without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty 3 micrograms/dose is administered intramuscularly after dilution as a primary course of 3 doses (0.2 mL each). It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 and 5.1).

If a child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty 3 micrograms/dose is administered intramuscularly after dilution as a single dose of 0.2 mL for infants and children 6 months to 4 years of age.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 6 months to 4 years

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Interchangeability

The primary course may consist of any previous or current Comirnaty vaccine but not exceeding the total number of doses required as primary course. The primary course should only be administered once.

The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers has not been established.

Paediatric population

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty 3 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty contain 10 doses of 0.2 mL of vaccine. In order to extract 10 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

In infants from 6 to less than 12 months of age, the recommended injection site is the anterolateral aspect of the thigh. In individuals 1 year of age and older, the recommended injection site is the anterolateral aspect of the thigh or the deltoid muscle.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Comirnaty 3 micrograms/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Summary of Product Characteristics for those formulations.

4.7 Effects on ability to drive and use machines

Comirnaty has no or negligible influence on the ability to drive, cycle, and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive, cycle, or use machines.

4.8 Undesirable effects

Summary of safety profile

Infants 6 to 23 months of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 2 176 infants (1 458 Comirnaty 3 mcg and 718 placebo) were 6 to 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 720 infants 6 to 23 months of age who received a 3-dose primary course (483 Comirnaty 3 mcg and 237 placebo) have been followed for a median of 1.7 months after the third dose.

The most frequent adverse reactions in infants 6 to 23 months of age that received any primary course dose included irritability (> 60%), drowsiness (> 40%), decreased appetite (> 30%), tenderness at the injection site (> 20%), injection site redness and fever (> 10%).

Children 2 to 4 years of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 3 541 children (2 368 Comirnaty 3 mcg and 1 173 placebo) were 2 to 4 years of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 1 268 children 2 to 4 years of age who received a 3-dose primary course (863 Comirnaty 3 mcg and 405 placebo) have been followed a median of 2.2 months after the third dose.

The most frequent adverse reactions in children 2 to 4 years of age that received any primary course dose included pain at injection site and fatigue (> 40%), injection site redness and fever (> 10%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of Comirnaty 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg

and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 50\%$), headache ($> 30\%$), injection site redness and swelling ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain ($> 60\%$), fatigue ($> 30\%$), headache ($> 20\%$), myalgia, chills, injection site redness and swelling ($> 10\%$).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills ($> 30\%$), arthralgia ($> 20\%$), pyrexia and injection site swelling ($> 10\%$) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for \geq 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Tabulated list of adverse reactions from clinical studies and post-authorisation experience in individuals 6 months of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common (\geq 1/10), Common (\geq 1/100 to < 1/10), Uncommon (\geq 1/1 000 to < 1/100), Rare (\geq 1/10 000 to < 1/1 000), Very rare (< 1/10 000), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty clinical trials and post-authorisation experience in individuals 6 months of age and older

| System Organ Class | Frequency | Adverse reactions |
|---|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash ⁱ , pruritus, urticaria, angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite ^j |
| Psychiatric disorders | Very common | Irritability ^k |
| | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache; drowsiness ^k |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ^l |

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| General disorders and administration site conditions | Very common | Injection site pain; injection site tenderness ^k ; fatigue; chills; pyrexia ^f ; Injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in participants 6 months to 11 years of age.
- The frequency category for rash was common in participants 6 to 23 months of age.
- The frequency category for decreased appetite was very common in participants 6 to 23 months of age.
- Irritability, injection site tenderness, and drowsiness pertain to participants 6 to 23 months of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 2.

Table 2. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a = 18 325 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 3.

Table 3. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N ^a =20 998 Cases n1 ^b Surveillance time ^c (n2 ^d) | Placebo N ^a =21 096 Cases n1 ^b Surveillance time ^c (n2 ^d) | Vaccine efficacy % (95% CI ^e) |
|-------------------------------|---|---|---|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 4) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 4. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1 ^a Surveillance time (n2 ^b) | Placebo Cases n1 ^a Surveillance time (n2 ^b) | Vaccine efficacy % (95% CI ^c) |
|----------------------------------|--|---|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.

f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.

g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of

1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 5. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 6.

Table 6. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^e) | GMT ^c (95% CI ^e) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month

after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroreponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroreponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroreponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroreponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroreponse rate is declared if the lower bound of the 2-sided 95% CI for the seroreponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 7.

Table 7. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| | Sampling time point ^a | | |
|--|---|---|---|
| | 1 month after booster dose (n ^b =67) GMT ^c (95% CI ^e) | 1 month after dose 2 (n ^b =96) GMT ^c (95% CI ^e) | 1 month after booster dose/ 1 month after dose 2 GMR ^d (95% CI ^d) |
| Assay | | | |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.

- d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Efficacy and immunogenicity of a 3-dose primary course in infants and children 6 months to 4 years of age

The efficacy analysis of Study 3 was performed across the combined population of participants 6 months through 4 years of age based on cases confirmed among 873 participants in the COVID-19 mRNA Vaccine group and 381 participants in the placebo group (2:1 randomization ratio) who received all 3 doses of study intervention during the blinded follow-up period when the Omicron variant of SARS-CoV-2 (BA.2) was the predominant variant in circulation (data cut-off date of 17 June 2022).

The vaccine efficacy results after Dose 3 in participants 6 months through 4 years of age are presented in Table 8.

Table 8. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Phase 2/3 – 6 Months to 4 Years of Age – Evaluable Efficacy (3-Dose) Population

| First COVID-19 occurrence from 7 days after Dose 3 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|--|---|--|
| Subgroup | COVID-19 mRNA Vaccine 3 mcg/Dose N^a=873 Cases n¹^b Surveillance Time^c (n2^d) | Placebo N^a=381 Cases n¹^b Surveillance Time^c (n2^d) | Vaccine Efficacy % (95% CI^e) |
| 6 months through 4 years ^e | 13 0.124 (794) | 21 0.054 (351) | 73.2 (43.8, 87.6) |
| 2 through 4 years | 9 0.081 (498) | 13 0.033 (204) | 71.8 (28.6, 89.4) |
| 6 months through 23 months | 4 0.042 (296) | 8 0.020 (147) | 75.8 (9.7, 94.7) |

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (i.e. negative N-binding antibody [serum] result at Dose 1, 1 month post-Dose 2 (if available), Dose 3 (if available) visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 3) and had no medical history of COVID-19 were included in the analysis.

- N = number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 3 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Vaccine efficacy in participants with or without prior SARS-CoV-2 infection was similar to those participants without prior SARS-CoV-2 infection.

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 12 cases (8 COVID-19 mRNA Vaccine and 4 placebo) among participants 6 months to 4 years of age. Among participants 6 months through 23 months of age, severe COVID-19 criteria were fulfilled for 3 cases (2 COVID-19 mRNA Vaccine and 1 placebo).

Immunogenicity analyses have been performed in the immunobridging subset of 82 Study 3 participants 6 to 23 months of age and 143 Study 3 participants 2 to 4 years of age without evidence of infection up to 1 month after Dose 3 based on a data cut-off date of 29 April 2022.

SARS-CoV-2 50% neutralising antibody titres (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 6 to 23 months of age and 2 to 4 years of age from Study 3 at 1 month after the 3-dose primary course and a randomly selected subset from Study 2 Phase 2/3 participants 16 to 25 years of age at 1 month after the 2-dose primary course, using a microneutralisation assay against the reference strain (USA_WA1/2020).

The primary immunobridging analyses compared the geometric mean titres (using a geometric mean ratio [GMR]) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 to 23 months of age and 2 to 4 years of age and up to 1 month after Dose 2 in participants 16 to 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference for both age groups (Table 9).

Table 9. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset - participants 6 months to 4 years of age (Study 3) 1 month after Dose 3 and participants 16 to 25 years of age (Study 2) 1 month after Dose 2 – without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | |
|--|----------------|---|-----------------------------|----------------|---|--|--|
| SARS-CoV-2 neutralization assay - NT50 (titre) ^c | | | | | | | |
| Age | N ^a | GMT ^b (95% CI ^b) (1 month after Dose 3) | Age | N ^a | GMT ^b (95% CI ^b) (1 month after Dose 2) | Age | GMR ^{c,d} (95% CI) |
| 2 to 4 years | 143 | 1 535.2 (1 388.2, 1 697.8) | 16 to 25 years of age | 170 | 1 180.0 (1 066.6, 1 305.4) | 2 to 4 years/16 to 25 years of age | 1.30 (1.13, 1.50) |
| 6 to 23 months | 82 | 1 406.5 (1 211.3, 1 633.1) | 16 to 25 years of age | 170 | 1 180.0 (1 066.6, 1 305.4) | 6 to 23 months years/16 to 25 years of age | 1.19 (1.00, 1.42) |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | |
| SARS-CoV-2 neutralization assay - NT50 (titre) ^c | | | | | | | |
| Age | N ^a | n ^f (%) (95% CI ^g) (1 month after Dose 3) | Age | N ^a | n ^f (%) (95% CI ^g) (1 month after Dose 2) | Age | Difference in seroresponse rates % ^h (95% CI ⁱ) ^j |
| 2 to 4 years | 141 | 141(100.0) (97.4, 100.0) | 16 to 25 years of age | 170 | 168 (98.8) (95.8, 99.9) | 2 to 4 years/16 to 25 years of age | 1.2 (1.5, 4.2) |
| 6 to 23 months | 80 | 80 (100.0) (95.5, 100.0) | 16 to 25 years of age | 170 | 168 (98.8) (95.8, 99.9) | 6 to 23 months years/16 to 25 years of age | 1.2 (3.4, 4.2) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [(i.e. N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- a. N = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point for GMTs and number of participants with valid and determinate assay results for the specified assay at both baseline and the given dose/sampling time point for seroresponse rates.
- b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (younger age group minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- d. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on GMR is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- f. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
- g. Exact 2-sided CI based on the Clopper and Pearson method.
- h. Difference in proportions, expressed as a percentage (younger age group minus 16 to 25 years of age).
- i. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- j. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

2 years when stored at -90 °C to -60 °C.

Within the 2-year shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 2-year shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, and within the 10 weeks storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

0.4 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a maroon flip-off plastic cap with aluminium seal. Each vial contains 10 doses, see section 6.6.

Pack size: 10 vials

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify that the vial has a maroon plastic cap and the product name is Comirnaty 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.

- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty for infants and children aged 6 months to 4 years. **Low dead-volume syringes and/or needles** should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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Fax: +49 6131 9084-2121
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial with a grey cap. Do not dilute prior to use.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of famtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Original). Famtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older

Comirnaty Original/Omicron BA.4-5 is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 12 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Paediatric population

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Elderly population

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

Single dose vials

Single dose vials of Comirnaty Original/Omicron BA.4-5 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty Original/Omicron BA.4-5.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty Original/Omicron BA.4-5 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Original/Omicron BA.4-5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

Comirnaty Original/Omicron BA.4-5 may be administered concomitantly with seasonal influenza vaccine.

Different injectable vaccines should be given at different injection sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Original/Omicron BA.4-5 can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty Original/Omicron BA.4-5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Original/Omicron BA.4-5 is inferred from safety data from Comirnaty and Omicron adapted vaccines.

Comirnaty 30 mcg

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills ($> 30\%$), arthralgia ($> 20\%$), pyrexia and injection site swelling ($> 10\%$) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia ($> 30\%$), chills and arthralgia ($> 20\%$).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these,

1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified (see section 5.1).

Omicron-adapted Comirnaty

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 micrograms) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain ($> 60\%$), fatigue ($> 50\%$), headache ($> 40\%$), muscle pain ($> 20\%$), chills ($> 10\%$), and joint pain ($> 10\%$).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 12 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--------------------------------------|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| | Uncommon | Hyperhidrosis; night sweats |

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|--|
| Skin and subcutaneous tissue disorder | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ^h |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Most cases appeared to be non-serious and temporary in nature.

Safety with concomitant vaccine administration

In Study 8, a Phase 3 study, participants 18 through 64 years of age who received Comirnaty coadministered with seasonal inactivated influenza vaccine (SIIV), quadrivalent followed 1 month later by placebo, were compared to participants who received an inactivated influenza vaccine with placebo followed 1 month later by Comirnaty alone (n=553 to 564 participants in each group). Reactogenicity events were reported more frequently by participants who received Comirnaty coadministered with SIIV, quadrivalent, compared to participants who received Comirnaty alone, but overall the reactogenicity events were mostly mild to moderate in severity. The most common adverse reactions reported in the coadministration group and after Comirnaty alone were injection site pain (86.2% and 84.4%, respectively), fatigue (64.0% and 50.8%, respectively) and headache (47.2% and 37.8%, respectively).

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 to 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 to 17 years of age, 18 to 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 2).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 to 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 to 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 2).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 3).

Table 2. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | |
|---|---|---|---------------------------|---|-----------------------------|---|--|--|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | n ^a | GMT ^c (95% CI ^e) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^e) | GMR ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | |
| SARS-CoV-2 neutralization assay | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) |
| Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥ 4 × LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 3. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference Strain – NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty 30 mcg

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 4.

Table 4. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n^{1b} Surveillance time^c (n^{2d}) | Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d}) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- N = Number of participants in the specified group.
 - n1 = Number of participants meeting the endpoint definition.
 - Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
 - n2 = Number of participants at risk for the endpoint.
 - Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N^a=20 998 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=21 096 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI)^e |
|-------------------------------|---|---|--|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- N = Number of participants in the specified group.
 - n1 = Number of participants meeting the endpoint definition.

- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 6) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 6. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI^c) |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.

b. n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Immunogenicity in participants 18 years of age and older – after booster dose

Effectiveness of a booster dose of Comirnaty was based on an assessment of 50% neutralizing antibody titres (NT50) against SARS-CoV-2 (USA_WA1/2020) in Study 2. In this study, the booster dose was administered 5 to 8 months (median 7 months) after the second dose. In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4 -fold rise in NT50 from baseline (before primary series). These analyses are summarized in Table 7.

Table 7. SARS-CoV-2 neutralization assay - NT50 (titre)[†] (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 through 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population[±]

| | n | 1 month after booster dose (95% CI) | 1 month after primary series (95% CI) | 1 month after booster dose - 1 month after primary series (97.5% CI) | Met noninferiority objective (Y/N) |
|---|------------------|--|---|--|------------------------------------|
| Geometric mean 50% neutralizing titre (GMT^b) | 212 ^a | 2 466.0 ^b (2 202.6, 2 760.8) | 755.7 ^b (663.1, 861.2) | 3.26 ^c (2.76, 3.86) | Y ^d |
| Seroresponse rate (%) for 50% neutralizing titre[†] | 200 ^e | 199 ^f 99.5% (97.2%, 100.0%) | 190 ^f 95.0% (91.0%, 97.6%) | 4.5% ^g (1.0%, 7.9% ^h) | Y ⁱ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

[†] SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of Comirnaty) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

[±] All eligible participants who had received 2 doses of Comirnaty as initially randomised, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Comirnaty, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

- n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
- Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80 .
- n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
- Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
- Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
- Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.

Relative vaccine efficacy in participants 16 years of age and older – after booster dose

An interim efficacy analysis of Study 4, a placebo-controlled booster study performed in approximately 10 000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up.

The booster dose was administered 5 to 13 months (median 11 months) after the second dose. Vaccine efficacy of the Comirnaty booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed.

The relative vaccine efficacy information for participants 16 years of age and older without prior evidence of SARS-CoV-2 infection is presented in Table 8. Relative vaccine efficacy in participants with or without evidence of prior SARS-CoV-2 infection was 94.6% (95% confidence interval of 88.5% to 97.9%), similar to that seen in those participants without evidence of prior infection. Primary COVID-19 cases observed from 7 days after booster vaccination were 7 primary cases in the Comirnaty group, and 124 primary cases in the placebo group.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after booster vaccination – participants 16 years of age and older without evidence of infection – evaluable efficacy population

| First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|--|--|---|
| | Comirnaty N^a=4 695 Cases n1^b Surveillance Time^c (n2^d) | Placebo N^a=4 671 Cases n1^b Surveillance Time^c (n2^d) | Relative Vaccine Efficacy^e % (95% CI^f) |
| First COVID-19 occurrence from 7 days after booster vaccination | 6 0.823 (4 659) | 123 0.792 (4 614) | 95.3 (89.5, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non-booster).
- f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Immunogenicity of a booster dose following primary vaccination with another authorised COVID-19 vaccine

Effectiveness of a Comirnaty booster dose (30 mcg) in individuals who completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose) is inferred from immunogenicity data from an independent National Institutes of Health (NIH) study phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States. In this study, adults (range 19 to 80 years of age) who had completed primary vaccination with Moderna 100 mcg 2-dose series (N = 51, mean age 54±17), Janssen single dose (N = 53, mean age 48±14), or Comirnaty 30 mcg 2-dose series (N = 50, mean age 50±18) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection received a booster dose of Comirnaty (30 mcg). The boost with Comirnaty induced a 36, 12, and 20 GMR-fold rise in neutralising titres following the Janssen, Moderna, and Comirnaty primary doses, respectively.

Heterologous boosting with Comirnaty was also evaluated in the CoV-BOOST study (EudraCT 2021-002175-19), a multicentre, randomised, controlled, phase 2 trial of third dose booster vaccination against COVID-19, in which 107 adult participants (median age 71 years of age,

interquartile range 54 to 77 years of age) were randomised at least 70 days post 2 doses of AstraZeneca COVID-19 Vaccine. After the AstraZeneca COVID-19 Vaccine primary series, pseudovirus (wild-type), neutralising antibody NT50 GMR-fold change increased 21.6-fold with heterologous Comirnaty booster (n = 95).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

2 years when stored at -90 °C to -60 °C.

Within the 2-year shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

Single dose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 2-year shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, within the 10-week storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Opened vials

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of

opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

Comirnaty Original/Omicron BA.4-5 dispersion is supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

Single dose vials pack size: 10 vials.

Multidose vials pack sizes: 10 vials or 195 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.

- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty Original/Omicron BA.4-5.
- Low dead-volume syringes and/or needles** should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
- Each dose must contain 0.3 mL of vaccine.
 - If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
 - Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
 An der Goldgrube 12
 55131 Mainz
 Germany
 Phone: +49 6131 9084-0
 Fax: +49 6131 9084-2121
 service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/014

Multidose vials

EU/1/20/1528/008
 EU/1/20/1528/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
 Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with an orange cap and must be diluted before use.

One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 5 micrograms of tozinameran and 5 micrograms of famtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Original). Famtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)

Comirnaty Original/Omicron BA.4-5 is administered intramuscularly after dilution as a single dose of 0.2 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty Original/Omicron BA.4-5 contain 10 doses of 0.2 mL of vaccine. In order to extract 10 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in individuals with weakened immune systems, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in individuals with weakened immune systems.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Original/Omicron BA.4-5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Original/Omicron BA.4-5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Original/Omicron BA.4-5 can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty Original/Omicron BA.4-5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Original/Omicron BA.4-5 is inferred from safety data from Comirnaty and Omicron adapted vaccines.

Comirnaty

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of the initially approved Comirnaty vaccine 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 50\%$), headache ($> 30\%$), injection site redness and swelling ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain (> 60%), fatigue (> 30%), headache (> 20%), myalgia, chills, injection site redness and swelling (> 10%).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 40%), chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose,

had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Omicron-adapted Comirnaty

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain ($> 60\%$), fatigue ($> 40\%$), headache ($> 20\%$), and muscle pain ($> 10\%$).

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 mcg) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain ($> 60\%$), fatigue ($> 50\%$), headache ($> 40\%$), muscle pain ($> 20\%$), chills ($> 10\%$), and joint pain ($> 10\%$).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 5 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 5 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|------------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ⁱ |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- a. In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- b. The frequency category for urticaria and angioedema was rare.
- c. Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- d. Adverse reaction determined post-authorisation.
- e. Refers to vaccinated arm.
- f. A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- g. Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- h. Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- i. Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 2.

Table 2. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Vaccine Group (as Assigned/Randomized) | | | | |
|--|----------------------------------|---|---|--|---|---|
| | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4 | | Study 3 Comirnaty 10 mcg Dose 3 and 1 Month After Dose 3 | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg |
| | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| Omicron BA.4-5 - NT50 (titre) ^e | Pre-vaccination | 102 | 488.3 (361.9, 658.8) | 112 | 248.3 (187.2, 329.5) | - |
| | 1 month | 102 | 2 189.9 (1 742.8, 2 751.7) | 113 | 1 393.6 (1 175.8, 1 651.7) | 1.12 (0.92, 1.37) |
| Reference strain - NT50 (titre) ^e | Pre-vaccination | 102 | 2 904.0 (2 372.6, 3 554.5) | 113 | 1 323.1 (1 055.7, 1 658.2) | - |
| | 1 month | 102 | 8 245.9 (7 108.9, 9 564.9) | 113 | 7 235.1 (6 331.5, 8 267.8) | - |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 through 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 4).

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | | |
|---|--|---|----------------------------|---|-----------------------------|---|--|--|-----------------------------------|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison | |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty | |
| | n ^a | GMT ^c (95% CI ^c) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^c) | GMR ^c (95% CI ^c) | |
| | Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g | |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | | |
| SARS-CoV-2 neutralization assay | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison | |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty | |
| | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) | |
| | Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥ 4 × LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

- e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 4. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference Strain – NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n^{1b} Surveillance time^c (n^{2d}) | Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d}) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N^a=20 998 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=21 096 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI^e) |
|-------------------------------|---|---|--|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.

- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a | Placebo Cases n1^a | Vaccine efficacy % (95% CI)^c |
|----------------------------------|---|---|--|
| | Surveillance time (n2^b) | Surveillance time (n2^b) | |
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- a. n1 = Number of participants meeting the endpoint definition.
- b. n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 8. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 9.

Table 9. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 10.

Table 10. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| | Sampling time point ^a | | 1 month after booster dose/ 1 month after dose 2 |
|--|---|--|---|
| | 1 month after booster dose (n ^b =67) | 1 month after dose 2 (n ^b =96) | |
| Assay | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils)

consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

2 years when stored at -90 °C to -60 °C.

Within the 2-year shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 2-year shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, and within the 10-week storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1.3 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and an orange flip-off plastic cap with aluminium seal. Each vial contains 10 doses, see section 6.6.

Pack sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- Verify that the vial has an **orange plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty Original/Omicron BA.4-5 for children aged 5 to 11 years. **Low dead-volume syringes and/or needles** should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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55131 Mainz
Germany
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/011
EU/1/20/1528/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial with a blue cap. Do not dilute prior to use.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

One dose (0.3 mL) contains 5 micrograms of tozinameran and 5 micrograms of famtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Original). Famtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

The vaccine is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)

Comirnaty Original/Omicron BA.4-5 is administered intramuscularly as a single dose of 0.3 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

Single dose vials

Single dose vials of Comirnaty Original/Omicron BA.4-5 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty Original/Omicron BA.4-5.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty Original/Omicron BA.4-5 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Original/Omicron BA.4-5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Original/Omicron BA.4-5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Original/Omicron BA.4-5 can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty Original/Omicron BA.4-5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Original/Omicron BA.4-5 is inferred from safety data from Comirnaty and Omicron adapted vaccines.

Comirnaty

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of the initially approved Comirnaty vaccine 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 50\%$), headache ($> 30\%$), injection site redness and swelling ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain ($> 60\%$), fatigue ($> 30\%$), headache ($> 20\%$), myalgia, chills, injection site redness and swelling ($> 10\%$).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills

(> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Omicron-adapted Comirnaty

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain (> 60%), fatigue (> 40%), headache (> 20%), and muscle pain (> 10%).

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 mcg) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain (> 60%), fatigue (> 50%), headache (> 40%), muscle pain (> 20%), chills (> 10%), and joint pain (> 10%).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 5 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 5 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ⁱ |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.

- i. Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 2.

Table 2. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Vaccine Group (as Assigned/Randomized) | | | | |
|--|----------------------------------|---|---|--|---|---|
| | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4 | | Study 3 Comirnaty 10 mcg Dose 3 and 1 Month After Dose 3 | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg |
| | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| Omicron BA.4-5 - NT50 (titre) ^e | Pre-vaccination | 102 | 488.3 (361.9, 658.8) | 112 | 248.3 (187.2, 329.5) | - |
| | 1 month | 102 | 2 189.9 (1 742.8, 2 751.7) | 113 | 1 393.6 (1 175.8, 1 651.7) | 1.12 (0.92, 1.37) |
| Reference strain - NT50 (titre) ^e | Pre-vaccination | 102 | 2 904.0 (2 372.6, 3 554.5) | 113 | 1 323.1 (1 055.7, 1 658.2) | - |
| | 1 month | 102 | 8 245.9 (7 108.9, 9 564.9) | 113 | 7 235.1 (6 331.5, 8 267.8) | - |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 through 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 4).

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | | |
|---|---|---|---------------------------|---|-----------------------------|---|--|--|--|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison | |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty | |
| | n ^a | GMT ^c (95% CI ^c) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^c) | GMR ^c (95% CI ^c) | |
| Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f | |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g | |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | | |
| | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison ≥ 56 years of age | |

| SARS-CoV-2 neutralization assay | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty |
|--|----------------------------|---|---------------------------|---|---------------------------|---|---|--|
| | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) |
| Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroreponse is defined as achieving a ≥ 4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥ 4 × LLOQ is considered a seroreponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8.
- N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- n = Number of participants with seroreponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage.
- 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, ≥ median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroreponse is > -10%.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroreponse is > -5%.

Table 4. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|--------------------------------------|--|----------------------------|--|---------------------------|--|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) |
| Reference Strain – NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a = 18 325 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N^a=20 998 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=21 096 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI^e) |
|-------------------------------|---|---|--|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1 ^a Surveillance time (n2 ^b) | Placebo Cases n1 ^a Surveillance time (n2 ^b) | Vaccine efficacy % (95% CI ^c) |
|----------------------------------|---|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.

f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.

g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of $>$ 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 8. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 9.

Table 9. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT

(nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3.

Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020).

Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 10.

Table 10. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| Assay | Sampling time point ^a | | 1 month after booster dose/ 1 month after dose 2 |
|--|---|--|---|
| | 1 month after booster dose (n ^b =67) | 1 month after dose 2 (n ^b =96) | |
| | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.

- d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Trometamol
Trometamol hydrochloride
Sucrose
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

18 months when stored at -90 °C to -60 °C.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

Single dose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 18-month shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, within the 10-week storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Opened vials

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

Comirnaty Original/Omicron BA.4-5 dispersion is supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a blue flip-off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

Single dose vials pack size: 10 vials.

Multidose vials pack size: 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **blue plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.

- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty Original/Omicron BA.4-5 for children aged 5 to 11 years.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
 An der Goldgrube 12
 55131 Mainz
 Germany
 Phone: +49 6131 9084-0
 Fax: +49 6131 9084-2121
 service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/015

Multidose vials

EU/1/20/1528/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with a maroon cap and must be diluted before use.

One vial (0.4 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 1.5 micrograms of tozinameran, and 1.5 micrograms of famtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Original). Famtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in infants and children aged 6 months to 4 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Infants and children 6 months to 4 years of age without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose is administered intramuscularly after dilution as a primary course of 3 doses (0.2 mL each). It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 and 5.1).

If a child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms or 1.5/1.5 micrograms dose level.

Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms/dose) is administered intramuscularly after dilution as a single dose of 0.2 mL for infants and children 6 months to 4 years of age.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 6 months to 4 years

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Interchangeability

The primary course may consist of any previous or current Comirnaty vaccine but not exceeding the total number of doses required as primary course. The primary course should only be administered once.

The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers has not been established.

Paediatric population

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty Original/Omicron BA.4-5 contain 10 doses of 0.2 mL of vaccine. In order to extract 10 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

In infants from 6 to less than 12 months of age, the recommended injection site is the anterolateral aspect of the thigh. In individuals 1 year of age and older, the recommended injection site is the anterolateral aspect of the thigh or the deltoid muscle.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Original/Omicron BA.4-5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Original/Omicron BA.4-5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Summary of Product Characteristics for those formulations.

4.7 Effects on ability to drive and use machines

Comirnaty Original/Omicron BA.4-5 has no or negligible influence on the ability to drive, cycle, and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive, cycle, or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of a dose of Comirnaty Original/Omicron BA.4-5 is inferred from safety data from Comirnaty and Omicron adapted vaccines.

Comirnaty

Infants 6 to 23 months of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 2 176 infants (1 458 initially approved Comirnaty 3 mcg and 718 placebo) were 6 to 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 720 infants 6 to 23 months of age who received a 3-dose primary course (483 Comirnaty 3 mcg and 237 placebo) have been followed for a median of 1.7 months after the third dose.

The most frequent adverse reactions in infants 6 to 23 months of age that received any primary course dose included irritability (> 60%), drowsiness (> 40%), decreased appetite (> 30%), tenderness at the injection site (> 20%), injection site redness and fever (> 10%).

Children 2 to 4 years of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 3 541 children (2 368 Comirnaty 3 mcg and 1 173 placebo) were 2 to 4 years of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 1 268 children 2 to 4 years of age who received a 3-dose primary course

(863 Comirnaty 3 mcg and 405 placebo) have been followed a median of 2.2 months after the third dose.

The most frequent adverse reactions in children 2 to 4 years of age that received any primary course dose included pain at injection site and fatigue (> 40%), injection site redness and fever (> 10%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of Comirnaty 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for \geq 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain (> 80%), fatigue (> 50%), headache (> 30%), injection site redness and swelling (\geq 20%), myalgia, chills and diarrhoea (> 10%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain (> 60%), fatigue (> 30%), headache (> 20%), myalgia, chills, injection site redness and swelling (> 10%).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for \geq 4 months after the second dose of Comirnaty.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for \geq 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 40%), chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia ($> 30\%$), chills and arthralgia ($> 20\%$).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Omicron-adapted Comirnaty

Infants 6 to 23 months of age – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 39 participants 6 to 23 months of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.1 to 8.6 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.7 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reaction in participants 6 to 23 months of age was irritability ($> 20\%$), decreased appetite ($> 10\%$), and drowsiness ($> 10\%$).

Children 2 to 4 years of age – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 124 participants 2 to 4 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.2 to 8.6 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.8 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 2 to 4 years of age were injection site pain ($> 30\%$) and fatigue ($> 20\%$).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)
 In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain (> 60%), fatigue (> 40%), headache (> 20%), and muscle pain (> 10%).

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 micrograms) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain (> 60%), fatigue (> 50%), headache (> 40%), muscle pain (> 20%), chills (> 10%), and joint pain (> 10%).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience in individuals 6 months of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1000$ to $< 1/100$), Rare ($\geq 1/10000$ to $< 1/1000$), Very rare ($< 1/10000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 6 months of age and older

| System Organ Class | Frequency | Adverse reactions |
|---|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash ⁱ , pruritus, urticaria, angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite ^j |
| Psychiatric disorders | Very common | Irritability ^k |
| | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache; drowsiness ^k |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ^l |
| General disorders and administration site conditions | Very common | Injection site pain; injection site tenderness ^k ; fatigue; chills; pyrexia ^f ; Injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in participants 6 months to 11 years of age.
- The frequency category for rash was common in participants 6 to 23 months of age.
- The frequency category for decreased appetite was very common in participants 6 to 23 months of age.
- Irritability, injection site tenderness, and drowsiness pertain to participants 6 to 23 months of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 – 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in infants and children 6 months to 4 years of age – after the booster (fourth dose)

In an analysis of a subset from Study 6, 60 participants 6 months to 4 years of age received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) after receiving 3 prior doses of Comirnaty 3 micrograms dose concentrate for dispersion. Results include immunogenicity data from a comparator subset of participants 6 months to 4 years of age in Study 3 who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion.

At 1 month after a booster dose (fourth dose), a booster dose with Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) elicited higher Omicron BA.4-5 specific neutralizing titres (regardless of baseline SARS-CoV-2 status) compared with the titres in the comparator group who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion. Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 6 months to 4 years of age are presented in Table 2.

Table 2. Geometric mean titres – Study 6 subset – participants with or without evidence of infection – 6 months through 4 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Age group | Sampling time point ^a | Vaccine group (as assigned/randomized) | | | |
|--|--------------------------|----------------------------------|---|--|---|--|
| | | | Study 6 Comirnaty Original/Omicron BA.4-5 1.5/1.5 mcg Dose 4 and 1 month after Dose 4 | | Study 3 Comirnaty 3 mcg Dose 3 and 1 month after Dose 3 | |
| | | | n ^b | GMT ^c (95% CI) ^e | n ^b | GMT ^c (95% CI) ^e |
| Omicron BA.4-5 - NT50 (titre) ^d | 6 months through 4 years | Pre-vaccination | 54 | 192.5 (120.4, 307.8) | 54 | 70.5 (51.1, 97.2) |
| | | 1 month | 58 | 1 695.2 (1 151.8, 2 494.9) | 54 | 607.9 (431.1, 857.2) |
| | | Pre-vaccination | 57 | 2 678.1 (1 913.0, 3 749.2) | 53 | 776.8 (536.4, 1 125.0) |

| SARS-CoV-2 neutralization assay | Age group | Sampling time point ^a | Vaccine group (as assigned/randomized) | | | |
|--|--------------------------|----------------------------------|---|--|--|--|
| | | | Study 6 Comirnaty Original/Omicron BA.4-5 1.5/1.5 mcg Dose 4 and 1 month after Dose 4 | | Study 3 Comirnaty 3 mcg Dose 3 and 1 month after Dose 3 | |
| | | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) |
| Reference strain - NT50 (titre) ^d | 6 months through 4 years | 1 month | 58 | 9 733.0 (7 708.2, 12 289.6) | 53 | 9 057.3 (7 223.4, 11 356.8) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 3.

Table 3. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Vaccine group (as assigned/randomized) | | | | |
|--|----------------------------------|---|---|--|---|---|
| | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 month after Dose 4 | | Study 3 Comirnaty 10 mcg Dose 3 and 1 month after Dose 3 | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | GMR ^d (95% CI ^d) |
| Omicron BA.4-5 - NT50 (titre) ^e | Pre-vaccination | 102 | 488.3 (361.9, 658.8) | 112 | 248.3 (187.2, 329.5) | - |
| | 1 month | 102 | 2 189.9 (1 742.8, 2 751.7) | 113 | 1 393.6 (1 175.8, 1 651.7) | 1.12 (0.92, 1.37) |
| Reference strain - NT50 (titre) ^e | Pre-vaccination | 102 | 2 904.0 (2 372.6, 3 554.5) | 113 | 1 323.1 (1 055.7, 1 658.2) | - |
| | 1 month | 102 | 8 245.9 (7 108.9, 9 564.9) | 113 | 7 235.1 (6 331.5, 8 267.8) | - |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 to 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 4).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 4).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 5).

Table 4. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | |
|---|---|---|---------------------------|---|-----------------------------|---|--|--|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | n ^a | GMT ^c (95% CI ^e) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^c) | GMR ^c (95% CI ^c) |
| Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | |
| SARS-CoV-2 neutralization assay | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) |
| Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥ 4 × LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 5. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference strain - NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n^{1b} Surveillance time^c (n^{2d}) | Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d}) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 7.

Table 7. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N ^a =20 998 Cases n1 ^b Surveillance time ^c (n2 ^d) | Placebo N ^a =21 096 Cases n1 ^b Surveillance time ^c (n2 ^d) | Vaccine efficacy % (95% CI ^e) |
|-------------------------------|---|---|---|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.

- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 8) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 8. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a | Placebo Cases n1^a | Vaccine efficacy % (95% CI)^c |
|----------------------------------|---|---|--|
| | Surveillance time (n2^b) | Surveillance time (n2^b) | |
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- a. n1 = Number of participants meeting the endpoint definition.
- b. n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 9. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 9. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 10.

Table 10. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 11.

Table 11. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| | Sampling time point ^a | | 1 month after booster dose/ 1 month after dose 2 |
|--|---|--|---|
| | 1 month after booster dose (n ^b =67) | 1 month after dose 2 (n ^b =96) | |
| Assay | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Efficacy and immunogenicity of a 3-dose primary course in infants and children 6 months to 4 years of age

The efficacy analysis of Study 3 was performed across the combined population of participants 6 months through 4 years of age based on cases confirmed among 873 participants in the COVID-19 mRNA Vaccine group and 381 participants in the placebo group (2:1 randomization ratio) who received all 3 doses of study intervention during the blinded follow-up period when the Omicron variant of SARS-CoV-2 (BA.2) was the predominant variant in circulation (data cut-off date of 17 June 2022).

The vaccine efficacy results after Dose 3 in participants 6 months through 4 years of age are presented in Table 12.

Table 12. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Phase 2/3 – 6 Months to 4 Years of Age – Evaluable Efficacy (3-Dose) Population

| First COVID-19 occurrence from 7 days after Dose 3 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|--|--|
| Subgroup | COVID-19 mRNA Vaccine 3 mcg/Dose N^a=873 Cases n1^b Surveillance Time^c (n2^d) | Placebo N^a=381 Cases n1^b Surveillance Time^c (n2^d) | Vaccine Efficacy % (95% CI^e) |
| 6 months through 4 years ^e | 13 0.124 (794) | 21 0.054 (351) | 73.2 (43.8, 87.6) |
| 2 through 4 years | 9 0.081 (498) | 13 0.033 (204) | 71.8 (28.6, 89.4) |
| 6 months through 23 months | 4 0.042 (296) | 8 0.020 (147) | 75.8 (9.7, 94.7) |

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (i.e. negative N-binding antibody [serum] result at Dose 1, 1 month post-Dose 2 (if available), Dose 3 (if available) visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 3) and had no medical history of COVID-19 were included in the analysis.

- N = number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 3 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Vaccine efficacy in participants with or without prior SARS-CoV-2 infection was similar to those participants without prior SARS-CoV-2 infection.

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 12 cases (8 COVID-19 mRNA Vaccine and 4 placebo) among participants 6 months to 4 years of age. Among participants 6 months through 23 months of age, severe COVID-19 criteria were fulfilled for 3 cases (2 COVID-19 mRNA Vaccine and 1 placebo).

Immunogenicity analyses have been performed in the immunobridging subset of 82 Study 3 participants 6 to 23 months of age and 143 Study 3 participants 2 to 4 years of age without evidence of infection up to 1 month after Dose 3 based on a data cut-off date of 29 April 2022.

SARS-CoV-2 50% neutralising antibody titres (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 6 to 23 months of age and 2 to 4 years of age from Study 3 at 1 month after the 3-dose primary course and a randomly selected subset from Study 2 Phase 2/3 participants 16 to 25 years of age at 1 month after the 2-dose primary course, using a microneutralisation assay against the reference strain (USA_WA1/2020).

The primary immunobridging analyses compared the geometric mean titres (using a geometric mean ratio [GMR]) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 to 23 months of age and 2 to 4 years of age and up to 1 month after Dose 2 in participants 16 to 25 years of age. The

prespecified immunobridging criteria were met for both the GMR and the seroresponse difference for both age groups (Table 13).

Table 13. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset - participants 6 months to 4 years of age (Study 3) 1 month after Dose 3 and participants 16 to 25 years of age (Study 2) 1 month after Dose 2 – without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | |
|---|----------------|---|-----------------------------|----------------|---|--|--|
| SARS-CoV-2 neutralization assay - NT50 (titre) ^e | | | | | | | |
| Age | N ^a | GMT ^b (95% CI ^b) (1 month after Dose 3) | Age | N ^a | GMT ^b (95% CI ^b) (1 month after Dose 2) | Age | GMR ^{c,d} (95% CI) |
| 2 to 4 years | 143 | 1 535.2 (1 388.2, 1 697.8) | 16 to 25 years of age | 170 | 1 180.0 (1 066.6, 1 305.4) | 2 to 4 years/16 to 25 years of age | 1.30 (1.13, 1.50) |
| 6 to 23 months | 82 | 1 406.5 (1 211.3, 1 633.1) | 16 to 25 years of age | 170 | 1 180.0 (1 066.6, 1 305.4) | 6 to 23 months years/16 to 25 years of age | 1.19 (1.00, 1.42) |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | |
| SARS-CoV-2 neutralization assay - NT50 (titre) ^e | | | | | | | |
| Age | N ^a | n ^f (%) (95% CI ^g) (1 month after Dose 3) | Age | N ^a | n ^f (%) (95% CI ^g) (1 month after Dose 2) | Age | Difference in seroresponse rates % ^h (95% CI) ^{i,j} |
| 2 to 4 years | 141 | 141(100.0) (97.4, 100.0) | 16 to 25 years of age | 170 | 168 (98.8) (95.8, 99.9) | 2 to 4 years/16 to 25 years of age | 1.2 (1.5, 4.2) |
| 6 to 23 months | 80 | 80 (100.0) (95.5, 100.0) | 16 to 25 years of age | 170 | 168 (98.8) (95.8, 99.9) | 6 to 23 months years/16 to 25 years of age | 1.2 (3.4, 4.2) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [(i.e. N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point for GMTs and number of participants with valid and determinate assay results for the specified assay at both baseline and the given dose/sampling time point for seroresponse rates.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.

- c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (younger age group minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- d. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on GMR is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- f. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
- g. Exact 2-sided CI based on the Clopper and Pearson method.
- h. Difference in proportions, expressed as a percentage (younger age group minus 16 to 25 years of age).
- i. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- j. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

2 years when stored at -90 °C to -60 °C.

Within the 2-year shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 2-year shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, and within the 10 weeks storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

0.4 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a maroon flip-off plastic cap with aluminium seal. Each vial contains 10 doses, see section 6.6.

Pack size: 10 vials

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Omicron/Original BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.

- The thawed vaccine must be diluted in its original vial with **2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty Original/Omicron BA.4-5 for infants and children aged 6 months to 4 years.
Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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55131 Mainz
Germany
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Fax: +49 6131 9084-2121
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection
 Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection in pre-filled syringe
 COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial, or a single dose pre-filled syringe. The single dose vial and multidose vial have a grey cap. Do not dilute prior to use.

Table 1. Comirnaty Omicron XBB.1.5 30 micrograms/dose qualitative and quantitative composition

| Product presentation | Container | Dose(s) per container (see sections 4.2 and 6.6) | Contents per dose |
|---|--------------------------|---|---|
| Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection | Single dose vial | 1 dose of 0.3 mL | One dose (0.3 mL) contains 30 micrograms of raxtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles). |
| | Multidose vial (2.25 mL) | 6 doses of 0.3 mL | |
| Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection in pre-filled syringe | Pre-filled syringe | 1 dose of 0.3 mL | |

Raxtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older

Comirnaty Omicron XBB.1.5 30 micrograms/dose is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 12 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Paediatric population

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Elderly population

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

Single dose vials

Single dose vials of Comirnaty Omicron XBB.1.5 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty Omicron XBB.1.5.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty Omicron XBB.1.5 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.

- Do not pool excess vaccine from multiple vials.

Pre-filled syringes

- Each single dose pre-filled syringe of Comirnaty Omicron XBB.1.5 contains 1 dose of 0.3 mL of vaccine.
- Attach a needle appropriate for intramuscular injection and administer the entire volume.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Omicron XBB.1.5 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Omicron XBB.1.5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

Comirnaty Omicron XBB.1.5 may be administered concomitantly with seasonal influenza vaccine.

Different injectable vaccines should be given at different injection sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Omicron XBB.1.5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty Omicron XBB.1.5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Omicron XBB.1.5 is inferred from safety data of the prior Comirnaty vaccines.

Comirnaty 30 mcg

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of the initially approved Comirnaty vaccine and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills ($> 30\%$), arthralgia ($> 20\%$), pyrexia and injection site swelling ($> 10\%$) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia ($> 30\%$), chills and arthralgia ($> 20\%$).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Participants 12 years of age and older – after subsequent booster doses

The safety of a booster dose of Comirnaty in participants 12 years of age and older is inferred from safety data from studies of a booster dose of Comirnaty in participants 18 years of age and older.

A subset of 325 adults 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 90 to 180 days after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of 1.4 months up to a data cut-off date of 11 March 2022. The most frequent adverse reactions in these participants were injection site pain ($> 70\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia and chills ($> 20\%$), and arthralgia ($> 10\%$).

In a subset from Study 4 (Phase 3), 305 adults > 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 5 to 12 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of at least 1.7 months up to a data cut-off date of 16 May 2022. The overall safety profile for the Comirnaty booster (fourth dose) was similar to that seen after the Comirnaty booster (third dose). The most frequent adverse reactions in participants > 55 years of age were injection site pain ($> 60\%$), fatigue ($> 40\%$), headache ($> 20\%$), myalgia and chills ($> 10\%$).

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified (see section 5.1).

Omicron-adapted Comirnaty

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 micrograms) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain ($> 60\%$), fatigue ($> 50\%$), headache ($> 40\%$), muscle pain ($> 20\%$), chills ($> 10\%$), and joint pain ($> 10\%$).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 2. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 12 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ^h |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Most cases appeared to be non-serious and temporary in nature.

Safety with concomitant vaccine administration

In Study 8, a Phase 3 study, participants 18 through 64 years of age who received Comirnaty coadministered with seasonal inactivated influenza vaccine (SIIV), quadrivalent followed 1 month

later by placebo, were compared to participants who received an inactivated influenza vaccine with placebo followed 1 month later by Comirnaty alone (n=553 to 564 participants in each group). Reactogenicity events were reported more frequently by participants who received Comirnaty coadministered with SIIV, quadrivalent, compared to participants who received Comirnaty alone, but overall the reactogenicity events were mostly mild to moderate in severity. The most common adverse reactions reported in the coadministration group and after Comirnaty alone were injection site pain (86.2% and 84.4%, respectively), fatigue (64.0% and 50.8%, respectively) and headache (47.2% and 37.8%, respectively).

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 to 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 to 17 years of age, 18 to 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 to 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 to 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 4).

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | |
|--|---|---|---------------------------|---|-----------------------------|---|--|--|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age ≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | n ^a | GMT ^c (95% CI ^e) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^e) | GMR ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g |

| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | |
|---|-----------------------------------|---|---------------------------|---|-----------------------------|---|--|---|
| | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison ≥ 56 years of age |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| SARS-CoV-2 neutralization assay | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) |
| Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage.
- 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 4. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference Strain – NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty 30 mcg

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a = 18 325 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N ^a =20 998 Cases n1 ^b Surveillance time ^c (n2 ^d) | Placebo N ^a =21 096 Cases n1 ^b Surveillance time ^c (n2 ^d) | Vaccine efficacy % (95% CI ^e) |
|-------------------------------|---|---|---|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI)^c |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
 - Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
 - Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
 - Significant acute renal, hepatic, or neurologic dysfunction;
 - Admission to an Intensive Care Unit;
 - Death.
- a. n1 = Number of participants meeting the endpoint definition.
b. n2 = Number of participants at risk for the endpoint.
c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Immunogenicity in participants 18 years of age and older – after booster dose

Effectiveness of a booster dose of Comirnaty was based on an assessment of 50% neutralizing antibody titres (NT50) against SARS-CoV-2 (USA_WA1/2020) in Study 2. In this study, the booster dose was administered 5 to 8 months (median 7 months) after the second dose. In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a \geq 4-fold rise in NT50 from baseline (before primary series). These analyses are summarized in Table 8.

Table 8. SARS-CoV-2 neutralization assay - NT50 (titre)[†] (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 through 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population[‡]

| | n | 1 month after booster dose (95% CI) | 1 month after primary series (95% CI) | 1 month after booster dose - 1 month after primary series (97.5% CI) | Met noninferiority objective (Y/N) |
|---|------------------|--|---|--|------------------------------------|
| Geometric mean 50% neutralizing titre (GMT^b) | 212 ^a | 2 466.0 ^b (2 202.6, 2 760.8) | 755.7 ^b (663.1, 861.2) | 3.26 ^c (2.76, 3.86) | Y ^d |
| Seroresponse rate (%) for 50% neutralizing titre[†] | 200 ^e | 199 ^f 99.5% (97.2%, 100.0%) | 190 ^f 95.0% (91.0%, 97.6%) | 4.5% ^g (1.0%, 7.9% ^h) | Y ⁱ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

[†] SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

- * Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of Comirnaty) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.
- ± All eligible participants who had received 2 doses of Comirnaty as initially randomised, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Comirnaty, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.
 - a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
 - b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
 - c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
 - d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80 .
 - e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
 - f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.
 - g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
 - h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
 - i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.

Relative vaccine efficacy in participants 16 years of age and older – after booster dose

An interim efficacy analysis of Study 4, a placebo-controlled booster study performed in approximately 10 000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up. The booster dose was administered 5 to 13 months (median 11 months) after the second dose. Vaccine efficacy of the Comirnaty booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed.

The relative vaccine efficacy information for participants 16 years of age and older without prior evidence of SARS-CoV-2 infection is presented in Table 9. Relative vaccine efficacy in participants with or without evidence of prior SARS-CoV-2 infection was 94.6% (95% confidence interval of 88.5% to 97.9%), similar to that seen in those participants without evidence of prior infection. Primary COVID-19 cases observed from 7 days after booster vaccination were 7 primary cases in the Comirnaty group, and 124 primary cases in the placebo group.

Table 9. Vaccine efficacy – First COVID-19 occurrence from 7 days after booster vaccination – participants 16 years of age and older without evidence of infection – evaluable efficacy population

| First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|--|--|---|
| | Comirnaty N^a=4 695 Cases n1^b Surveillance Time^c (n2^d) | Placebo N^a=4 671 Cases n1^b Surveillance Time^c (n2^d) | Relative Vaccine Efficacy^e % (95% CI^f) |
| First COVID-19 occurrence from 7 days after booster vaccination | 6 0.823 (4 659) | 123 0.792 (4 614) | 95.3 (89.5, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or

increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non-booster).
- f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Immunogenicity of a booster dose following primary vaccination with another authorised COVID-19 vaccine

Effectiveness of a Comirnaty booster dose (30 mcg) in individuals who completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose) is inferred from immunogenicity data from an independent National Institutes of Health (NIH) study phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States. In this study, adults (range 19 to 80 years of age) who had completed primary vaccination with Moderna 100 mcg 2-dose series (N = 51, mean age 54±17), Janssen single dose (N = 53, mean age 48±14), or Comirnaty 30 mcg 2-dose series (N = 50, mean age 50±18) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection received a booster dose of Comirnaty (30 mcg). The boost with Comirnaty induced a 36, 12, and 20 GMR-fold rise in neutralising titres following the Janssen, Moderna, and Comirnaty primary doses, respectively.

Heterologous boosting with Comirnaty was also evaluated in the CoV-BOOST study (EudraCT 2021-002175-19), a multicentre, randomised, controlled, phase 2 trial of third dose booster vaccination against COVID-19, in which 107 adult participants (median age 71 years of age, interquartile range 54 to 77 years of age) were randomised at least 70 days post 2 doses of AstraZeneca COVID-19 Vaccine. After the AstraZeneca COVID-19 Vaccine primary series, pseudovirus (wild-type), neutralising antibody NT50 GMR-fold change increased 21.6-fold with heterologous Comirnaty booster (n = 95).

Immunogenicity in participants > 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)

In an interim analysis of a subset from Study 4 (Substudy E), 305 participants > 55 years of age who had completed a series of 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 5 to 12 months after receiving Dose 3. For the Immunogenicity subset data see Table 7.

Immunogenicity in participants 18 to ≤ 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 325 participants 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 90 to 180 days after receiving Dose 3. For the Immunogenicity subset data see Table 10.

Table 10. Summary of immunogenicity data from participants in C4591031 Substudy D (cohort 2 full expanded set) and Substudy E (expanded cohort immunogenicity subset) who received Comirnaty 30 mcg as booster (fourth dose) – participants without evidence of infection up to 1 month after booster dose – evaluable immunogenicity population

| | Dose/ sampling time point ^a | Substudy D (18 to ≤ 55 years of age) Comirnaty 30 mcg | | Substudy E (> 55 years of age) Comirnaty 30 mcg | |
|--|--|---|--|---|--|
| | | N ^b | GMT (95% CI ^d) | N ^b | GMT (95% CI ^d) |
| GMT | | | | | |
| SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre) | 1/Prevax | 226 | 315.0 (269.0, 368.9) | 167 | 67.5 (52.9, 86.3) |
| | 1/1 Month | 228 | 1 063.2 (935.8, 1 207.9) | 163 | 455.8 (365.9, 567.6) |
| SARS-CoV-2 neutralization assay – reference strain – NT50 (titre) | 1/Prevax | 226 | 3 999.0 (3 529.5, 4 531.0) | 179 | 1 389.1 (1 142.1, 1 689.5) |
| | 1/1 Month | 227 | 12 009.9 (10 744.3, 13 424.6) | 182 | 5 998.1 (5 223.6, 6 887.4) |
| Seroresponse rate at 1 month post-Dose 4 | | N ^c | n ^e (%) (95% CI ^f) | N ^c | n ^e (%) (95% CI ^f) |
| SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre) | 1/1 Month | 226 | 91 (40.3%) (33.8, 47.0) | 149 | 85 (57.0%) (48.7, 65.1) |
| SARS-CoV-2 neutralization assay – reference strain – NT50 (titre) | 1/1 Month | 225 | 76 (33.8%) (27.6, 40.4) | 179 | 88 (49.2%) (41.6, 56.7) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Median time from Dose 3 to Dose 4 of Comirnaty 30 mcg is 4.0 months for Substudy D Cohort 2 and 6.3 months for Substudy E expanded cohort.

Note: Substudy D Full Expanded Set = Cohort 2 excluding the sentinel group; Substudy E Immunogenicity Subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving ≥ 4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the post-vaccination measure of ≥ 4 × LLOQ is considered a seroresponse.

- Protocol-specified timing for blood sample collection.
- N = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Vials

Unopened vials

The vaccine will be received frozen at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Frozen vaccine can be stored either at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$ or $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ upon receipt.

18 months when stored at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for up to 10 weeks.

Thawing procedure

Single dose vials

When stored frozen at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$, 10-vial packs of single dose vials of the vaccine can be thawed at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for 2 hours or individual vials can be thawed at room temperature (up to $30\text{ }^{\circ}\text{C}$) for 30 minutes.

Multidose vials

When stored frozen at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$, 10-vial packs of multidose vials of the vaccine can be thawed at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for 6 hours or individual vials can be thawed at room temperature (up to $30\text{ }^{\circ}\text{C}$) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ within the 18-month shelf life.

- Upon moving the vaccine to $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ it should be stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between $8\text{ }^{\circ}\text{C}$ and $30\text{ }^{\circ}\text{C}$.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from $-2\text{ }^{\circ}\text{C}$ to $2\text{ }^{\circ}\text{C}$, within the 10-week storage period between $2\text{ }^{\circ}\text{C}$ and $8\text{ }^{\circ}\text{C}$.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of $8\text{ }^{\circ}\text{C}$ to $30\text{ }^{\circ}\text{C}$, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Opened vials

Chemical and physical in-use stability has been demonstrated for 12 hours at $2\text{ }^{\circ}\text{C}$ to $30\text{ }^{\circ}\text{C}$, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Pre-filled syringes

Confirm the storage conditions listed for the different types of pre-filled syringes.

Plastic pre-filled syringes

The vaccine will be received frozen at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Frozen vaccine can be stored either at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$ or $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ upon receipt.

12 months when stored at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Within the 12-month shelf life the thawed (previously frozen) pre-filled syringes may be stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for up to 10 weeks.

Thawing procedure for plastic pre-filled syringes

Frozen 10-pack of pre-filled syringes should be thawed in the original carton at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for 2 hours or at room temperature (up to $30\text{ }^{\circ}\text{C}$) for 60 minutes.

Thawed (previously frozen) plastic pre-filled syringes

10 weeks storage and transport at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ within the 12-month shelf life.

- Upon moving the vaccine to $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ it should be stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, thawed pre-filled syringes can be stored for up to 12 hours at temperatures between $8\text{ }^{\circ}\text{C}$ and $30\text{ }^{\circ}\text{C}$ and can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

The following information is intended to guide healthcare professionals only in case of temporary temperature excursion.

If an individual frozen pre-filled syringe is thawed at room temperature (up to $30\text{ }^{\circ}\text{C}$) outside of the carton, the pre-filled syringe should not be stored and should be used immediately.

Stability data indicate that the pre-filled syringe is stable for up to 10 weeks when stored at temperatures from $-2\text{ }^{\circ}\text{C}$ to $2\text{ }^{\circ}\text{C}$, within the 10-week storage period between $2\text{ }^{\circ}\text{C}$ and $8\text{ }^{\circ}\text{C}$.

Glass pre-filled syringes

The vaccine will be received and stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ (refrigerated only).

8 months when stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$.

Prior to use, pre-filled syringes can be stored for up to 12 hours at temperatures between $8\text{ }^{\circ}\text{C}$ and $30\text{ }^{\circ}\text{C}$ and can be handled in room light conditions.

6.4 Special precautions for storage

Vials and plastic pre-filled syringes

Store single dose vials, multidose vials and frozen plastic pre-filled syringes in a freezer at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Glass pre-filled syringes

Store glass pre-filled syringes at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$. DO NOT FREEZE.

Vials and pre-filled syringes

Store the vaccine in the original package in order to protect from light. During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

Single dose and multidose vials

Supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

Single dose vials pack size: 10 vials.

Multidose vials pack sizes: 10 vials or 195 vials.

Not all pack sizes may be marketed.

Pre-filled syringes

Plastic pre-filled syringes

Supplied in a single dose pre-filled syringe (1 mL long cyclic-olefin copolymer plastic syringe) with plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber) without needle.

Pack size: 10 pre-filled syringes.

Glass pre-filled syringes

Supplied in a single dose glass pre-filled syringe (type I glass syringe) with plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber) without needle.

Pack size: 10 pre-filled syringes

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

Instructions applicable to single dose and multidose vials

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.

- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty Omicron XBB.1.5.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the multidose vial. Discard any unused vaccine 12 hours after first puncture.

Instructions applicable to pre-filled syringes

Plastic pre-filled syringes

- Frozen pre-filled syringes must be completely thawed prior to use.
 - A 10 pre-filled syringe pack can be thawed at 2 °C to 8 °C. It may take 2 hours to thaw.
 - Alternatively, a carton of 10 frozen pre-filled syringes may be thawed for 60 minutes at room temperature (up to 30 °C).
- If an individual pre-filled syringe is thawed outside the carton at room temperature (up to 30 °C), this must be used immediately.
- Upon moving the pre-filled syringes to 2 °C to 8 °C storage, update the expiry date on the carton. If received at 2 °C to 8 °C, check that the expiry date has been updated.
- Thawed (previously frozen) pre-filled syringes can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). Once thawed, the vaccine cannot be re-frozen.
- Prior to use, the thawed pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.
- Remove tip cap by slowly turning the cap counterclockwise. Do not shake. Attach a needle appropriate for intramuscular injection and administer the entire volume.

Glass pre-filled syringes

- Prior to use, pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.

- Remove tip cap by slowly turning the cap counterclockwise. Do not shake. Attach a needle appropriate for intramuscular injection and administer the entire volume.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/018

Multidose vials

EU/1/20/1528/019
EU/1/20/1528/020

Plastic pre-filled syringes

EU/1/20/1528/025

Glass pre-filled syringes

EU/1/20/1528/027

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with an orange cap and must be diluted before use.

One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 10 micrograms of raxtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Raxtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)

Comirnaty Omicron XBB.1.5 10 micrograms/dose is administered intramuscularly after dilution as a single dose of 0.2 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Comirnaty Omicron XBB.1.5 10 micrograms/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty Omicron XBB.1.5 contain 10 doses of 0.2 mL of vaccine. In order to extract 10 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Omicron XBB.1.5 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Omicron XBB.1.5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Omicron XBB.1.5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Omicron XBB.1.5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty Omicron XBB.1.5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Omicron XBB.1.5 is inferred from safety data of the prior Comirnaty vaccine.

Comirnaty

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of the initially approved Comirnaty vaccine 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 50\%$), headache ($> 30\%$), injection site redness and swelling ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain (> 60%), fatigue (> 30%), headache (> 20%), myalgia, chills, injection site redness and swelling (> 10%).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 40%), chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose,

had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Omicron-adapted Comirnaty

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain ($> 60\%$), fatigue ($> 40\%$), headache ($> 20\%$), and muscle pain ($> 10\%$).

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 mcg) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain ($> 60\%$), fatigue ($> 50\%$), headache ($> 40\%$), muscle pain ($> 20\%$), chills ($> 10\%$), and joint pain ($> 10\%$).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 5 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 5 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ⁱ |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 – 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 – 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 2.

Table 2. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Vaccine Group (as Assigned/Randomized) | | | | |
|--|----------------------------------|---|---|--|---|---|
| | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4 | | Study 3 Comirnaty 10 mcg Dose 3 and 1 Month After Dose 3 | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg |
| | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| Omicron BA.4-5 - NT50 (titre) ^e | Pre-vaccination | 102 | 488.3 (361.9, 658.8) | 112 | 248.3 (187.2, 329.5) | - |
| | 1 month | 102 | 2 189.9 (1 742.8, 2 751.7) | 113 | 1 393.6 (1 175.8, 1 651.7) | 1.12 (0.92, 1.37) |
| Reference strain - NT50 (titre) ^e | Pre-vaccination | 102 | 2 904.0 (2 372.6, 3 554.5) | 113 | 1 323.1 (1 055.7, 1 658.2) | - |
| | 1 month | 102 | 8 245.9 (7 108.9, 9 564.9) | 113 | 7 235.1 (6 331.5, 8 267.8) | - |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 through 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 4).

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | | |
|---|--|---|----------------------------|---|-----------------------------|---|--|--|-----------------------------------|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison | |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty | |
| | n ^a | GMT ^c (95% CI ^c) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^c) | GMR ^c (95% CI ^c) | |
| | Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g | |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | | |
| SARS-CoV-2 neutralization assay | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison | |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty | |
| | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) | |
| | Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥ 4 × LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

- e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 4. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference Strain – NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a = 18 325 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N ^a =20 998 Cases n1 ^b Surveillance time ^c (n2 ^d) | Placebo N ^a =21 096 Cases n1 ^b Surveillance time ^c (n2 ^d) | Vaccine efficacy % (95% CI ^e) |
|-------------------------------|---|---|---|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.

- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI)^c |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- a. n1 = Number of participants meeting the endpoint definition.
- b. n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 8. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 9.

Table 9. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 10.

Table 10. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| Assay | Sampling time point ^a | | 1 month after booster dose/ 1 month after dose 2 |
|--|---|--|---|
| | 1 month after booster dose (n ^b =67) | 1 month after dose 2 (n ^b =96) | |
| | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils)

consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

18 months when stored at -90 °C to -60 °C.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 18-month shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, and within the 10-week storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1.3 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and an orange flip-off plastic cap with aluminium seal. Each vial contains 10 doses, see section 6.6.

Pack size: 10 vials

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- Verify that the vial has an **orange plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty Omicron XBB.1.5 for children aged 5 to 11 years. **Low dead-volume syringes and/or needles** should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial with a blue cap. Do not dilute prior to use.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

One dose (0.3 mL) contains 10 micrograms of raxtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Raxtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

The vaccine is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)

Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection is administered intramuscularly as a single dose of 0.3 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Comirnaty Omicron XBB.1.5 10 micrograms/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

Single dose vials

Single dose vials of Comirnaty Omicron XBB.1.5 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty Omicron XBB.1.5.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty Omicron XBB.1.5 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Omicron XBB.1.5 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Omicron XBB.1.5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Omicron XBB.1.5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Omicron XBB.1.5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty Omicron XBB.1.5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Omicron XBB.1.5 is inferred from safety data of the prior Comirnaty vaccine.

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of the initially approved Comirnaty vaccine 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 50\%$), headache ($> 30\%$), injection site redness and swelling ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain ($> 60\%$), fatigue ($> 30\%$), headache ($> 20\%$), myalgia, chills, injection site redness and swelling ($> 10\%$).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills ($> 30\%$), arthralgia ($> 20\%$), pyrexia and injection site swelling ($> 10\%$) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia ($> 30\%$), chills and arthralgia ($> 20\%$).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Omicron-adapted Comirnaty

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain ($> 60\%$), fatigue ($> 40\%$), headache ($> 20\%$), and muscle pain ($> 10\%$).

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 mcg) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain ($> 60\%$), fatigue ($> 50\%$), headache ($> 40\%$), muscle pain ($> 20\%$), chills ($> 10\%$), and joint pain ($> 10\%$).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 5 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 5 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ⁱ |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset

of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 2.

Table 2. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Vaccine Group (as Assigned/Randomized) | | | | |
|--|----------------------------------|---|---|--|---|---|
| | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4 | | Study 3 Comirnaty 10 mcg Dose 3 and 1 Month After Dose 3 | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg |
| | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| Omicron BA.4-5 - NT50 (titre) ^e | Pre-vaccination | 102 | 488.3 (361.9, 658.8) | 112 | 248.3 (187.2, 329.5) | - |
| | 1 month | 102 | 2 189.9 (1 742.8, 2 751.7) | 113 | 1 393.6 (1 175.8, 1 651.7) | 1.12 (0.92, 1.37) |
| Reference strain - NT50 (titre) ^e | Pre-vaccination | 102 | 2 904.0 (2 372.6, 3 554.5) | 113 | 1 323.1 (1 055.7, 1 658.2) | - |
| | 1 month | 102 | 8 245.9 (7 108.9, 9 564.9) | 113 | 7 235.1 (6 331.5, 8 267.8) | - |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 through 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty

Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 4).

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | |
|---|---|---|---------------------------|---|-----------------------------|---|--|--|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age ≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | n ^a | GMT ^c (95% CI ^c) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^c) | GMR ^c (95% CI ^c) |
| Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | |
| SARS-CoV-2 neutralization assay | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) |
| Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage.
- 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category ($<$ median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 4. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference Strain – NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a = 18 325 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N ^a =20 998 Cases n1 ^b Surveillance time ^c (n2 ^d) | Placebo N ^a =21 096 Cases n1 ^b Surveillance time ^c (n2 ^d) | Vaccine efficacy % (95% CI ^e) |
|-------------------------------|---|---|--|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI^c) |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.

f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.

g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of $>$ 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 8. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 9.

Table 9. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ⁱ) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3.

Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020).

Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 10.

Table 10. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| | Sampling time point ^a | | |
|--|---|---|---|
| | 1 month after booster dose (n ^b =67) | 1 month after dose 2 (n ^b =96) | 1 month after booster dose/ 1 month after dose 2 |
| Assay | GMT ^c (95% CI) | GMT ^c (95% CI) | GMR ^d (95% CI ^d) |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

18 months when stored at -90 °C to -60 °C.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

Single dose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 18-month shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, within the 10-week storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Opened vials

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

Comirnaty Omicron XBB.1.5 dispersion is supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a blue flip-off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

Single dose vials pack size: 10 vials.

Multidose vials pack size: 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **blue plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).

- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty Omicron XBB.1.5 for children aged 5 to 11 years.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
 An der Goldgrube 12
 55131 Mainz
 Germany
 Phone: +49 6131 9084-0
 Fax: +49 6131 9084-2121
 service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/022

Multidose vials

EU/1/20/1528/023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

| Container | Doses per container (see sections 4.2 and 6.6) | Content per dose |
|--|---|--|
| Multidose vial (0.4 mL) (maroon cap) | 10 doses of 0.2 mL after dilution | One dose (0.2 mL) contains 3 micrograms of raxtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles). |
| Multidose vial (0.48 mL) (yellow cap) | 3 doses of 0.3 mL after dilution | One dose (0.3 mL) contains 3 micrograms of raxtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles). |

Raxtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in infants and children aged 6 months to 4 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Infants and children 6 months to 4 years of age without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty Omicron XBB.1.5 3 micrograms/dose is administered intramuscularly after dilution as a primary course of 3 doses. It is recommended to administer the second dose 3 weeks after the first

dose followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 and 5.1).

If a child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty Omicron XBB.1.5 3 micrograms/dose is administered intramuscularly after dilution as a single dose for infants and children 6 months to 4 years of age.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 6 months to 4 years

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Interchangeability

The primary course may consist of any previous or current Comirnaty vaccine but not exceeding the total number of doses required as primary course. The primary course should only be administered once.

The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers has not been established.

Paediatric population

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

Maroon cap (10-dose vial)

After dilution, vials with a **maroon cap** of Comirnaty Omicron XBB.1.5 contain **10 doses of 0.2 mL** of vaccine. In order to extract 10 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain **0.2 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.2 mL**, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Yellow cap (3-dose vial)

After dilution, vials with a **yellow cap** of Comirnaty Omicron XBB.1.5 contain **3 doses of 0.3 mL** of vaccine. Standard syringes and needles can be used to extract 3 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

In infants from 6 to less than 12 months of age, the recommended injection site is the anterolateral aspect of the thigh. In individuals 1 year of age and older, the recommended injection site is the anterolateral aspect of the thigh or the deltoid muscle.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Omicron XBB.1.5 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Omicron XBB.1.5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Omicron XBB.1.5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Summary of Product Characteristics for those formulations.

4.7 Effects on ability to drive and use machines

Comirnaty Omicron XBB.1.5 has no or negligible influence on the ability to drive, cycle, and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive, cycle, or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Omicron XBB.1.5 is inferred from safety data of the prior Comirnaty vaccines.

Comirnaty

Infants 6 to 23 months of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 2 176 infants (1 458 initially approved Comirnaty 3 mcg and 718 placebo) were 6 to 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 720 infants 6 to 23 months of age who received a

3-dose primary course (483 Comirnaty 3 mcg and 237 placebo) have been followed for a median of 1.7 months after the third dose.

The most frequent adverse reactions in infants 6 to 23 months of age that received any primary course dose included irritability (> 60%), drowsiness (> 40%), decreased appetite (> 30%), tenderness at the injection site (> 20%), injection site redness and fever (> 10%).

Children 2 to 4 years of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 3 541 children (2 368 Comirnaty 3 mcg and 1 173 placebo) were 2 to 4 years of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 1 268 children 2 to 4 years of age who received a 3-dose primary course (863 Comirnaty 3 mcg and 405 placebo) have been followed a median of 2.2 months after the third dose.

The most frequent adverse reactions in children 2 to 4 years of age that received any primary course dose included pain at injection site and fatigue (> 40%), injection site redness and fever (> 10%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of Comirnaty 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain (> 80%), fatigue (> 50%), headache (> 30%), injection site redness and swelling ($\geq 20\%$), myalgia, chills and diarrhoea (> 10%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain (> 60%), fatigue (> 30%), headache (> 20%), myalgia, chills, injection site redness and swelling (> 10%).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills ($> 30\%$), arthralgia ($> 20\%$), pyrexia and injection site swelling ($> 10\%$) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia ($> 30\%$), chills and arthralgia ($> 20\%$).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Omicron-adapted Comirnaty

Infants 6 to 23 months of age – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 39 participants 6 to 23 months of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.1 to 8.6 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.7 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reaction in participants 6 to 23 months of age was irritability ($> 20\%$), decreased appetite ($> 10\%$), and drowsiness ($> 10\%$).

Children 2 to 4 years of age – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 124 participants 2 to 4 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.2 to 8.6 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.8 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 2 to 4 years of age were injection site pain (> 30%) and fatigue (> 20%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain (> 60%), fatigue (> 40%), headache (> 20%), and muscle pain (> 10%).

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 micrograms) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain (> 60%), fatigue (> 50%), headache (> 40%), muscle pain (> 20%), chills (> 10%), and joint pain (> 10%).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 6 months of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 6 months of age and older

| System Organ Class | Frequency | Adverse reactions |
|--------------------------------------|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash ⁱ , pruritus, urticaria, angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite ^j |
| Psychiatric disorders | Very common | Irritability ^k |
| | Uncommon | Insomnia |

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Nervous system disorders | Very common | Headache; drowsiness ^k |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ^l |
| General disorders and administration site conditions | Very common | Injection site pain; injection site tenderness ^k ; fatigue; chills; pyrexia ^f ; Injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in participants 6 months to 11 years of age.
- The frequency category for rash was common in participants 6 to 23 months of age.
- The frequency category for decreased appetite was very common in participants 6 to 23 months of age.
- Irritability, injection site tenderness, and drowsiness pertain to participants 6 to 23 months of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in infants and children 6 months to 4 years of age – after the booster (fourth dose)

In an analysis of a subset from Study 6, 60 participants 6 months to 4 years of age received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) after receiving 3 prior doses of Comirnaty 3 micrograms dose concentrate for dispersion. Results include immunogenicity data from a comparator subset of participants 6 months to 4 years of age in Study 3 who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion.

At 1 month after a booster dose (fourth dose), a booster dose with Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) elicited higher Omicron BA.4-5 specific neutralizing titres (regardless of baseline SARS-CoV-2 status) compared with the titres in the comparator group who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion. Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 6 months to 4 years of age are presented in Table 2.

Table 2. Geometric mean titres – Study 6 subset – participants with or without evidence of infection – 6 months through 4 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Age group | Sampling time point ^a | Vaccine group (as assigned/randomized) | | | |
|--|--------------------------|----------------------------------|--|--|--|--|
| | | | Study 6 Comirnaty Original/Omicron BA.4-5 1.5/1.5 mcg Dose 4 and 1 month after Dose 4 | | Study 3 Comirnaty 3 mcg Dose 3 and 1 month after Dose 3 | |
| | | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) |
| Omicron BA.4-5 - NT50 (titre) ^d | 6 months through 4 years | Pre-vaccination | 54 | 192.5 (120.4, 307.8) | 54 | 70.5 (51.1, 97.2) |
| | | 1 month | 58 | 1 695.2 (1 151.8, 2 494.9) | 54 | 607.9 (431.1, 857.2) |
| Reference strain - NT50 (titre) ^d | 6 months through 4 years | Pre-vaccination | 57 | 2 678.1 (1 913.0, 3 749.2) | 53 | 776.8 (536.4, 1 125.0) |
| | | 1 month | 58 | 9 733.0 (7 708.2, 12 289.6) | 53 | 9 057.3 (7 223.4, 11 356.8) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 3.

Table 3. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Vaccine group (as assigned/randomized) | | | | |
|--|----------------------------------|---|---|--|---|---|
| | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 month after Dose 4 | | Study 3 Comirnaty 10 mcg Dose 3 and 1 month after Dose 3 | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | GMR ^d (95% CI ^d) |
| Omicron BA.4-5 - NT50 (titre) ^e | Pre-vaccination | 102 | 488.3 (361.9, 658.8) | 112 | 248.3 (187.2, 329.5) | - |
| | 1 month | 102 | 2 189.9 (1 742.8, 2 751.7) | 113 | 1 393.6 (1 175.8, 1 651.7) | 1.12 (0.92, 1.37) |
| Reference strain - NT50 (titre) ^e | Pre-vaccination | 102 | 2 904.0 (2 372.6, 3 554.5) | 113 | 1 323.1 (1 055.7, 1 658.2) | - |
| | 1 month | 102 | 8 245.9 (7 108.9, 9 564.9) | 113 | 7 235.1 (6 331.5, 8 267.8) | - |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 to 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 4).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 4).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 5).

Table 4. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | |
|---|---|---|---------------------------|---|-----------------------------|---|--|--|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | n ^a | GMT ^c (95% CI ^e) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^c) | GMR ^c (95% CI ^c) |
| Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | |
| SARS-CoV-2 neutralization assay | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) |
| Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥ 4 × LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 5. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference strain - NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n^{1b} Surveillance time^c (n^{2d}) | Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d}) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 7.

Table 7. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N ^a =20 998 Cases n1 ^b Surveillance time ^c (n2 ^d) | Placebo N ^a =21 096 Cases n1 ^b Surveillance time ^c (n2 ^d) | Vaccine efficacy % (95% CI ^e) |
|-------------------------------|---|---|---|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.

- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 8) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 8. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI)^c |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- a. n1 = Number of participants meeting the endpoint definition.
- b. n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 9. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 9. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 10.

Table 10. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 11.

Table 11. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| Assay | Sampling time point ^a | | 1 month after booster dose/ 1 month after dose 2 GMR ^d (95% CI ^d) |
|--|---|---|---|
| | 1 month after booster dose (n ^b =67) GMT ^c (95% CI ^c) | 1 month after dose 2 (n ^b =96) GMT ^c (95% CI ^c) | |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Efficacy and immunogenicity of a 3-dose primary course in infants and children 6 months to 4 years of age

The efficacy analysis of Study 3 was performed across the combined population of participants 6 months through 4 years of age based on cases confirmed among 873 participants in the COVID-19 mRNA Vaccine group and 381 participants in the placebo group (2:1 randomization ratio) who received all 3 doses of study intervention during the blinded follow-up period when the Omicron variant of SARS-CoV-2 (BA.2) was the predominant variant in circulation (data cut-off date of 17 June 2022).

The vaccine efficacy results after Dose 3 in participants 6 months through 4 years of age are presented in Table 12.

Table 12. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Phase 2/3 – 6 Months to 4 Years of Age – Evaluable Efficacy (3-Dose) Population

| First COVID-19 occurrence from 7 days after Dose 3 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|--|--|
| Subgroup | COVID-19 mRNA Vaccine 3 mcg/Dose N^a=873 Cases n¹^b Surveillance Time^c (n²^d) | Placebo N^a=381 Cases n¹^b Surveillance Time^c (n²^d) | Vaccine Efficacy % (95% CI)^e |
| 6 months through 4 years ^e | 13 0.124 (794) | 21 0.054 (351) | 73.2 (43.8, 87.6) |
| 2 through 4 years | 9 0.081 (498) | 13 0.033 (204) | 71.8 (28.6, 89.4) |
| 6 months through 23 months | 4 0.042 (296) | 8 0.020 (147) | 75.8 (9.7, 94.7) |

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (i.e. negative N-binding antibody [serum] result at Dose 1, 1 month post-Dose 2 (if available), Dose 3 (if available) visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 3) and had no medical history of COVID-19 were included in the analysis.

- N = number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 3 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Vaccine efficacy in participants with or without prior SARS-CoV-2 infection was similar to those participants without prior SARS-CoV-2 infection.

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 12 cases (8 COVID-19 mRNA Vaccine and 4 placebo) among participants 6 months to 4 years of age. Among participants 6 months through 23 months of age, severe COVID-19 criteria were fulfilled for 3 cases (2 COVID-19 mRNA Vaccine and 1 placebo).

Immunogenicity analyses have been performed in the immunobridging subset of 82 Study 3 participants 6 to 23 months of age and 143 Study 3 participants 2 to 4 years of age without evidence of infection up to 1 month after Dose 3 based on a data cut-off date of 29 April 2022.

SARS-CoV-2 50% neutralising antibody titres (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 6 to 23 months of age and 2 to 4 years of age from Study 3 at 1 month after the 3-dose primary course and a randomly selected subset from Study 2 Phase 2/3 participants 16 to 25 years of age at 1 month after the 2-dose primary course, using a microneutralisation assay against the reference strain (USA_WA1/2020).

The primary immunobridging analyses compared the geometric mean titres (using a geometric mean ratio [GMR]) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 to 23 months of age and 2 to 4 years of age and up to 1 month after Dose 2 in participants 16 to 25 years of age. The

prespecified immunobridging criteria were met for both the GMR and the seroresponse difference for both age groups (Table 13).

Table 13. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset - participants 6 months to 4 years of age (Study 3) 1 month after Dose 3 and participants 16 to 25 years of age (Study 2) 1 month after Dose 2 – without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | |
|---|----------------|---|-----------------------------|----------------|---|--|--|
| SARS-CoV-2 neutralization assay - NT50 (titre) ^e | | | | | | | |
| Age | N ^a | GMT ^b (95% CI ^b) (1 month after Dose 3) | Age | N ^a | GMT ^b (95% CI ^b) (1 month after Dose 2) | Age | GMR ^{c,d} (95% CI) |
| 2 to 4 years | 143 | 1 535.2 (1 388.2, 1 697.8) | 16 to 25 years of age | 170 | 1 180.0 (1 066.6, 1 305.4) | 2 to 4 years/16 to 25 years of age | 1.30 (1.13, 1.50) |
| 6 to 23 months | 82 | 1 406.5 (1 211.3, 1 633.1) | 16 to 25 years of age | 170 | 1 180.0 (1 066.6, 1 305.4) | 6 to 23 months years/16 to 25 years of age | 1.19 (1.00, 1.42) |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | |
| SARS-CoV-2 neutralization assay - NT50 (titre) ^e | | | | | | | |
| Age | N ^a | n ^f (%) (95% CI ^g) (1 month after Dose 3) | Age | N ^a | n ^f (%) (95% CI ^g) (1 month after Dose 2) | Age | Difference in seroresponse rates % ^h (95% CI) ^j |
| 2 to 4 years | 141 | 141(100.0) (97.4, 100.0) | 16 to 25 years of age | 170 | 168 (98.8) (95.8, 99.9) | 2 to 4 years/16 to 25 years of age | 1.2 (1.5, 4.2) |
| 6 to 23 months | 80 | 80 (100.0) (95.5, 100.0) | 16 to 25 years of age | 170 | 168 (98.8) (95.8, 99.9) | 6 to 23 months years/16 to 25 years of age | 1.2 (3.4, 4.2) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [(i.e. N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point for GMTs and number of participants with valid and determinate assay results for the specified assay at both baseline and the given dose/sampling time point for seroresponse rates.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.

- c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (younger age group minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- d. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on GMR is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- f. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
- g. Exact 2-sided CI based on the Clopper and Pearson method.
- h. Difference in proportions, expressed as a percentage (younger age group minus 16 to 25 years of age).
- i. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- j. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

18 months when stored at -90 °C to -60 °C.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 18-month shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, and within the 10 weeks storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Maroon cap (10-dose vial)

0.4 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a **maroon flip-off plastic cap** with aluminium seal. Each vial contains **10 doses**, see section 6.6.

Pack size: 10 vials

Yellow cap (3-dose vial)

0.48 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a **yellow flip-off plastic cap** with aluminium seal. Each vial contains **3 doses**, see section 6.6.

Pack size: 10 vials

6.6 Special precautions for disposal and other handling

Maroon cap (10-dose vial)

Handling instructions prior to use for a vial with a maroon cap

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label or a different cap colour, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.

- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution for a vial with a maroon cap

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses using a vial with a maroon cap

- After dilution, the vial contains 2.6 mL from which **10 doses** of **0.2 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw **0.2 mL** of Comirnaty Omicron XBB.1.5 for infants and children aged 6 months to 4 years.
Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain **0.2 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.2 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Yellow cap (3-dose vial)

Handling instructions prior to use for a vial with a yellow cap

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **yellow plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label, or a different cap colour, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution for a vial with a yellow cap

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.1 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.1 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.3 mL doses using a vial with a yellow cap

- After dilution, the vial contains 1.58 mL from which **3 doses** of **0.3 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw **0.3 mL** of Comirnaty Omicron XBB.1.5 for infants and children aged 6 months to 4 years. **Standard syringes and/or needles** can be used in order to extract 3 doses from a single vial.
- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
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55131 Mainz
Germany
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Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

Maroon cap (10-dose vial)

EU/1/20/1528/024

Yellow cap (3-dose vial)

EU/1/20/1528/026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty JN.1 30 micrograms/dose dispersion for injection
 Comirnaty JN.1 30 micrograms/dose dispersion for injection in pre-filled syringe
 COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial, or a single dose pre-filled syringe. The single dose vial and multidose vial have a grey cap. Do not dilute prior to use.

Table 1. Comirnaty JN.1 30 micrograms/dose qualitative and quantitative composition

| Product presentation | Container | Dose(s) per container (see sections 4.2 and 6.6) | Contents per dose |
|---|-----------------------------|---|---|
| Comirnaty JN.1 30 micrograms/dose dispersion for injection | Single dose vial | 1 dose of 0.3 mL | One dose (0.3 mL) contains 30 micrograms of bretovameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles). |
| | Multidose vial (2.25 mL) | 6 doses of 0.3 mL | |
| Comirnaty JN.1 30 micrograms/dose dispersion for injection in pre-filled syringe | Pre-filled syringe | 1 dose of 0.3 mL | |

Bretovameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron JN.1).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty JN.1 30 micrograms/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older

Comirnaty JN.1 30 micrograms/dose is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 12 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Paediatric population

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Elderly population

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty JN.1 30 micrograms/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

Single dose vials

Single dose vials of Comirnaty JN.1 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty JN.1.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty JN.1 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.

- Do not pool excess vaccine from multiple vials.

Pre-filled syringes

- Each single dose pre-filled syringe of Comirnaty JN.1 contains 1 dose of 0.3 mL of vaccine.
- Attach a needle appropriate for intramuscular injection and administer the entire volume.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty JN.1 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty JN.1 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

Comirnaty JN.1 may be administered concomitantly with seasonal influenza vaccine.

Different injectable vaccines should be given at different injection sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty JN.1 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty JN.1 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty JN.1 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty JN.1 can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty JN.1 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty JN.1 is inferred from safety data of the prior Comirnaty vaccines.

Comirnaty 30 mcg

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of the initially approved Comirnaty vaccine and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills ($> 30\%$), arthralgia ($> 20\%$), pyrexia and injection site swelling ($> 10\%$) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia ($> 30\%$), chills and arthralgia ($> 20\%$).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Participants 12 years of age and older – after subsequent booster doses

The safety of a booster dose of Comirnaty in participants 12 years of age and older is inferred from safety data from studies of a booster dose of Comirnaty in participants 18 years of age and older.

A subset of 325 adults 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 90 to 180 days after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of 1.4 months up to a data cut-off date of 11 March 2022. The most frequent adverse reactions in these participants were injection site pain ($> 70\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia and chills ($> 20\%$), and arthralgia ($> 10\%$).

In a subset from Study 4 (Phase 3), 305 adults > 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 5 to 12 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of at least 1.7 months up to a data cut-off date of 16 May 2022. The overall safety profile for the Comirnaty booster (fourth dose) was similar to that seen after the Comirnaty booster (third dose). The most frequent adverse reactions in participants > 55 years of age were injection site pain ($> 60\%$), fatigue ($> 40\%$), headache ($> 20\%$), myalgia and chills ($> 10\%$).

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified (see section 5.1).

Omicron-adapted Comirnaty

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 micrograms) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain ($> 60\%$), fatigue ($> 50\%$), headache ($> 40\%$), muscle pain ($> 20\%$), chills ($> 10\%$), and joint pain ($> 10\%$).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 2. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 12 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ^h |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Most cases appeared to be non-serious and temporary in nature.

Safety with concomitant vaccine administration

In Study 8, a Phase 3 study, participants 18 through 64 years of age who received Comirnaty coadministered with seasonal inactivated influenza vaccine (SIIV), quadrivalent followed 1 month

later by placebo, were compared to participants who received an inactivated influenza vaccine with placebo followed 1 month later by Comirnaty alone (n= 553 to 564 participants in each group). Reactogenicity events were reported more frequently by participants who received Comirnaty coadministered with SIIV, quadrivalent, compared to participants who received Comirnaty alone, but overall the reactogenicity events were mostly mild to moderate in severity. The most common adverse reactions reported in the coadministration group and after Comirnaty alone were injection site pain (86.2% and 84.4%, respectively), fatigue (64.0% and 50.8%, respectively) and headache (47.2% and 37.8%, respectively).

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 to 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 to 17 years of age, 18 to 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 to 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 to 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 4).

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | |
|--|---|---|---------------------------|---|-----------------------------|---|--|--|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | n ^a | GMT ^c (95% CI ^e) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^e) | GMR ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g |

| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | |
|---|-----------------------------------|---|---------------------------|---|-----------------------------|---|---|---|
| | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison ≥ 56 years of age |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| SARS-CoV-2 neutralization assay | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) |
| Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage.
- 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category ($<$ median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 4. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|--|----------------------------|--|---------------------------|--|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI) ^c | n ^b | GMT ^c (95% CI) ^c | n ^b | GMT ^c (95% CI) ^c |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference Strain – NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty 30 mcg

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n^{1b} Surveillance time^c (n^{2d}) | Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d}) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N^a=20 998 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=21 096 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI^e) |
|-------------------------------|---|---|--|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI^c) |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.

f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.

g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without

evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Immunogenicity in participants 18 years of age and older – after booster dose

Effectiveness of a booster dose of Comirnaty was based on an assessment of 50% neutralizing antibody titres (NT50) against SARS-CoV-2 (USA_WA1/2020) in Study 2. In this study, the booster dose was administered 5 to 8 months (median 7 months) after the second dose. In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4-fold rise in NT50 from baseline (before primary series). These analyses are summarized in Table 8.

Table 8. SARS-CoV-2 neutralization assay - NT50 (titre)[†] (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 through 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population[‡]

| | n | 1 month after booster dose (95% CI) | 1 month after primary series (95% CI) | 1 month after booster dose - 1 month after primary series (97.5% CI) | Met noninferiority objective (Y/N) |
|---|------------------|--|---|--|------------------------------------|
| Geometric mean 50% neutralizing titre (GMT)^b | 212 ^a | 2 466.0 ^b (2 202.6, 2 760.8) | 755.7 ^b (663.1, 861.2) | 3.26 ^c (2.76, 3.86) | Y ^d |
| Seroresponse rate (%) for 50% neutralizing titre[†] | 200 ^e | 199 ^f 99.5% (97.2%, 100.0%) | 190 ^f 95.0% (91.0%, 97.6%) | 4.5% ^g (1.0%, 7.9% ^h) | Y ⁱ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

- † SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.
- * Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of Comirnaty) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.
- ± All eligible participants who had received 2 doses of Comirnaty as initially randomised, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Comirnaty, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.
 - a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
 - b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
 - c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
 - d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80 .
 - e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
 - f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.
 - g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
 - h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
 - i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.

Relative vaccine efficacy in participants 16 years of age and older – after booster dose

An interim efficacy analysis of Study 4, a placebo-controlled booster study performed in approximately 10 000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up. The booster dose was administered 5 to 13 months (median 11 months) after the second dose. Vaccine efficacy of the Comirnaty booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed.

The relative vaccine efficacy information for participants 16 years of age and older without prior evidence of SARS-CoV-2 infection is presented in Table 9. Relative vaccine efficacy in participants with or without evidence of prior SARS-CoV-2 infection was 94.6% (95% confidence interval of 88.5% to 97.9%), similar to that seen in those participants without evidence of prior infection. Primary COVID-19 cases observed from 7 days after booster vaccination were 7 primary cases in the Comirnaty group, and 124 primary cases in the placebo group.

Table 9. Vaccine efficacy – First COVID-19 occurrence from 7 days after booster vaccination – participants 16 years of age and older without evidence of infection – evaluable efficacy population

| First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|--|--|---|
| | Comirnaty N^a=4 695 Cases n1^b Surveillance Time^c (n2^d) | Placebo N^a=4 671 Cases n1^b Surveillance Time^c (n2^d) | Relative Vaccine Efficacy^e % (95% CI^f) |
| First COVID-19 occurrence from 7 days after booster vaccination | 6 0.823 (4 659) | 123 0.792 (4 614) | 95.3 (89.5, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non-booster).
- Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Immunogenicity of a booster dose following primary vaccination with another authorised COVID-19 vaccine

Effectiveness of a Comirnaty booster dose (30 mcg) in individuals who completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose) is inferred from immunogenicity data from an independent National Institutes of Health (NIH) study phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States. In this study, adults (range 19 to 80 years of age) who had completed primary vaccination with Moderna 100 mcg 2-dose series (N = 51, mean age 54±17), Janssen single dose (N = 53, mean age 48±14), or Comirnaty 30 mcg 2-dose series (N = 50, mean age 50±18) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection received a booster dose of Comirnaty (30 mcg). The boost with Comirnaty induced a 36, 12, and 20 GMR-fold rise in neutralising titres following the Janssen, Moderna, and Comirnaty primary doses, respectively.

Heterologous boosting with Comirnaty was also evaluated in the CoV-BOOST study (EudraCT 2021-002175-19), a multicentre, randomised, controlled, phase 2 trial of third dose booster vaccination against COVID-19, in which 107 adult participants (median age 71 years of age, interquartile range 54 to 77 years of age) were randomised at least 70 days post 2 doses of AstraZeneca COVID-19 Vaccine. After the AstraZeneca COVID-19 Vaccine primary series, pseudovirus (wild-type), neutralising antibody NT50 GMR-fold change increased 21.6-fold with heterologous Comirnaty booster (n = 95).

Immunogenicity in participants > 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)

In an interim analysis of a subset from Study 4 (Substudy E), 305 participants > 55 years of age who had completed a series of 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 5 to 12 months after receiving Dose 3. For the Immunogenicity subset data see Table 7.

Immunogenicity in participants 18 to ≤ 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 325 participants 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 90 to 180 days after receiving Dose 3. For the Immunogenicity subset data see Table 10.

Table 10. Summary of immunogenicity data from participants in C4591031 Substudy D (cohort 2 full expanded set) and Substudy E (expanded cohort immunogenicity subset) who received Comirnaty 30 mcg as booster (fourth dose) – participants without evidence of infection up to 1 month after booster dose – evaluable immunogenicity population

| | Dose/ sampling time point ^a | Substudy D (18 to ≤ 55 years of age) Comirnaty 30 mcg | | Substudy E (> 55 years of age) Comirnaty 30 mcg | |
|--|--|---|--|---|--|
| | | N ^b | GMT (95% CI ^d) | N ^b | GMT (95% CI ^d) |
| GMT | | | | | |
| SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre) | 1/Prevax | 226 | 315.0 (269.0, 368.9) | 167 | 67.5 (52.9, 86.3) |
| | 1/1 Month | 228 | 1 063.2 (935.8, 1 207.9) | 163 | 455.8 (365.9, 567.6) |
| SARS-CoV-2 neutralization assay – reference strain – NT50 (titre) | 1/Prevax | 226 | 3 999.0 (3 529.5, 4 531.0) | 179 | 1 389.1 (1 142.1, 1 689.5) |
| | 1/1 Month | 227 | 12 009.9 (10 744.3, 13 424.6) | 182 | 5 998.1 (5 223.6, 6 887.4) |
| Seroresponse rate at 1 month post-Dose 4 | | N ^c | n ^e (%) (95% CI ^f) | N ^c | n ^e (%) (95% CI ^f) |
| SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre) | 1/1 Month | 226 | 91 (40.3%) (33.8, 47.0) | 149 | 85 (57.0%) (48.7, 65.1) |
| SARS-CoV-2 neutralization assay – reference strain – NT50 (titre) | 1/1 Month | 225 | 76 (33.8%) (27.6, 40.4) | 179 | 88 (49.2%) (41.6, 56.7) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Median time from Dose 3 to Dose 4 of Comirnaty 30 mcg is 4.0 months for Substudy D Cohort 2 and 6.3 months for Substudy E expanded cohort.

Note: Substudy D Full Expanded Set = Cohort 2 excluding the sentinel group; Substudy E Immunogenicity Subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving ≥ 4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the post-vaccination measure of ≥ 4 × LLOQ is considered a seroresponse.

a. Protocol-specified timing for blood sample collection.

b. N = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.

c. N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.

d. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

- e. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- f. Exact 2-sided CI, based on the Clopper and Pearson method.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Vials

Unopened vials

The vaccine will be received frozen at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Frozen vaccine can be stored either at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$ or $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ upon receipt.

18 months when stored at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for up to 10 weeks.

Thawing procedure

Single dose vials

When stored frozen at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$, 10-vial packs of single dose vials of the vaccine can be thawed at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for 2 hours or individual vials can be thawed at room temperature (up to $30\text{ }^{\circ}\text{C}$) for 30 minutes.

Multidose vials

When stored frozen at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$, 10-vial packs of multidose vials of the vaccine can be thawed at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for 6 hours or individual vials can be thawed at room temperature (up to $30\text{ }^{\circ}\text{C}$) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ within the 18-month shelf life.

- Upon moving the vaccine to $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ it should be stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between $8\text{ }^{\circ}\text{C}$ and $30\text{ }^{\circ}\text{C}$.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from $-2\text{ }^{\circ}\text{C}$ to $2\text{ }^{\circ}\text{C}$, within the 10-week storage period between $2\text{ }^{\circ}\text{C}$ and $8\text{ }^{\circ}\text{C}$.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of $8\text{ }^{\circ}\text{C}$ to $30\text{ }^{\circ}\text{C}$, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Opened vials

Chemical and physical in-use stability has been demonstrated for 12 hours at $2\text{ }^{\circ}\text{C}$ to $30\text{ }^{\circ}\text{C}$, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of

opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Pre-filled syringes

Confirm the storage conditions listed for the different types of pre-filled syringes.

Plastic pre-filled syringes

The vaccine will be received frozen at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Frozen vaccine can be stored either at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$ or $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ upon receipt.

12 months when stored at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Within the 12-month shelf life the thawed (previously frozen) pre-filled syringes may be stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for up to 10 weeks.

Thawing procedure for plastic pre-filled syringes

Frozen 10-pack of pre-filled syringes should be thawed in the original carton at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for 2 hours or at room temperature (up to $30\text{ }^{\circ}\text{C}$) for 60 minutes.

Thawed (previously frozen) plastic pre-filled syringes

10 weeks storage and transport at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ within the 12-month shelf life.

- Upon moving the vaccine to $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ it should be stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, thawed pre-filled syringes can be stored for up to 12 hours at temperatures between $8\text{ }^{\circ}\text{C}$ and $30\text{ }^{\circ}\text{C}$ and can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

The following information is intended to guide healthcare professionals only in case of temporary temperature excursion.

If an individual frozen pre-filled syringe is thawed at room temperature (up to $30\text{ }^{\circ}\text{C}$) outside of the carton, the pre-filled syringe should not be stored and should be used immediately.

Stability data indicate that the pre-filled syringe is stable for up to 10 weeks when stored at temperatures from $-2\text{ }^{\circ}\text{C}$ to $2\text{ }^{\circ}\text{C}$, within the 10-week storage period between $2\text{ }^{\circ}\text{C}$ and $8\text{ }^{\circ}\text{C}$.

Glass pre-filled syringes

The vaccine will be received and stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ (refrigerated only).

8 months when stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$.

Prior to use, pre-filled syringes can be stored for up to 12 hours at temperatures between $8\text{ }^{\circ}\text{C}$ and $30\text{ }^{\circ}\text{C}$ and can be handled in room light conditions.

6.4 Special precautions for storage

Vials and plastic pre-filled syringes

Store single dose vials, multidose vials and frozen plastic pre-filled syringes in a freezer at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Glass pre-filled syringes

Store glass pre-filled syringes at 2 °C to 8 °C. DO NOT FREEZE.

Vials and pre-filled syringes

Store the vaccine in the original package in order to protect from light. During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

Single dose and multidose vials

Supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

Single dose vials pack size: 10 vials.

Multidose vials pack size: 10 vials.

Not all pack sizes may be marketed.

Pre-filled syringes

Plastic pre-filled syringes

Supplied in a single dose pre-filled syringe (1 mL long cyclic-olefin copolymer plastic syringe) with plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber) without needle.

Pack size: 10 pre-filled syringes.

Glass pre-filled syringes

Supplied in a single dose glass pre-filled syringe (type I glass syringe) with plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber) without needle.

Pack size: 10 pre-filled syringes

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

Instructions applicable to single dose and multidose vials

- **Verify that the vial has a grey plastic cap and the product name is Comirnaty JN.1 30 micrograms/dose dispersion for injection (12 years and older).**
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.

- Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
- Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty JN.1.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the multidose vial. Discard any unused vaccine 12 hours after first puncture.

Instructions applicable to pre-filled syringes

Plastic pre-filled syringes

- Frozen pre-filled syringes must be completely thawed prior to use.
 - A 10 pre-filled syringe pack can be thawed at 2 °C to 8 °C. It may take 2 hours to thaw.
 - Alternatively, a carton of 10 frozen pre-filled syringes may be thawed for 60 minutes at room temperature (up to 30 °C).
- If an individual pre-filled syringe is thawed outside the carton at room temperature (up to 30 °C), this must be used immediately.
- Upon moving the pre-filled syringes to 2 °C to 8 °C storage, update the expiry date on the carton. If received at 2 °C to 8 °C, check that the expiry date has been updated.
- Thawed (previously frozen) pre-filled syringes can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). Once thawed, the vaccine cannot be re-frozen.
- Prior to use, the thawed pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.
- Remove tip cap by slowly turning the cap counterclockwise. Do not shake. Attach a needle appropriate for intramuscular injection and administer the entire volume.

Glass pre-filled syringes

- Prior to use, pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.
- Remove tip cap by slowly turning the cap counterclockwise. Do not shake. Attach a needle appropriate for intramuscular injection and administer the entire volume.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/028

Multidose vials

EU/1/20/1528/029

Plastic pre-filled syringes

EU/1/20/1528/031

Glass pre-filled syringes

EU/1/20/1528/030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with an orange cap and must be diluted before use.

One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 10 micrograms of bretovameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Bretovameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron JN.1).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)

Comirnaty JN.1 10 micrograms/dose is administered intramuscularly after dilution as a single dose of 0.2 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Comirnaty JN.1 10 micrograms/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty contain 10 doses of 0.2 mL of vaccine. In order to extract 10 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty JN.1 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty JN.1 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty JN.1 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty JN.1 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty JN.1 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty JN.1 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty JN.1 can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty JN.1 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty JN.1 is inferred from safety data of the prior Comirnaty vaccine.

Comirnaty

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of the initially approved Comirnaty vaccine 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 50\%$), headache ($> 30\%$), injection site redness and swelling ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series.

The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain (> 60%), fatigue (> 30%), headache (> 20%), myalgia, chills, injection site redness and swelling (> 10%).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 40%), chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these,

1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Omicron-adapted Comirnaty

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain ($> 60\%$), fatigue ($> 40\%$), headache ($> 20\%$), and muscle pain ($> 10\%$).

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 mcg) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain ($> 60\%$), fatigue ($> 50\%$), headache ($> 40\%$), muscle pain ($> 20\%$), chills ($> 10\%$), and joint pain ($> 10\%$).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 5 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 5 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--------------------------------------|-----------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|--|
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ⁱ |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 – 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 – 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 2.

Table 2. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Vaccine Group (as Assigned/Randomized) | | | | |
|--|----------------------------------|---|---|--|---|---|
| | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4 | | Study 3 Comirnaty 10 mcg Dose 3 and 1 Month After Dose 3 | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | GMR ^d (95% CI ^d) |
| Omicron BA.4-5 - NT50 (titre) ^e | Pre-vaccination | 102 | 488.3 (361.9, 658.8) | 112 | 248.3 (187.2, 329.5) | - |
| | 1 month | 102 | 2 189.9 (1 742.8, 2 751.7) | 113 | 1 393.6 (1 175.8, 1 651.7) | 1.12 (0.92, 1.37) |
| Reference strain - NT50 (titre) ^e | Pre-vaccination | 102 | 2 904.0 (2 372.6, 3 554.5) | 113 | 1 323.1 (1 055.7, 1 658.2) | - |
| | 1 month | 102 | 8 245.9 (7 108.9, 9 564.9) | 113 | 7 235.1 (6 331.5, 8 267.8) | - |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 through 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 4).

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | |
|---|---|---|---------------------------|---|-----------------------------|---|--|--|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | n ^a | GMT ^c (95% CI ^e) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^e) | GMR ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | |
| SARS-CoV-2 neutralization assay | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) |
| Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥ 4 × LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 4. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference Strain – NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a = 18 325 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N ^a =20 998 Cases n1 ^b Surveillance time ^c (n2 ^d) | Placebo N ^a =21 096 Cases n1 ^b Surveillance time ^c (n2 ^d) | Vaccine efficacy % (95% CI ^e) |
|-------------------------------|---|---|---|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.

- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI)^c |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- a. n1 = Number of participants meeting the endpoint definition.
- b. n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 8. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 9.

Table 9. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 10.

Table 10. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| Assay | Sampling time point ^a | | 1 month after booster dose/ 1 month after dose 2 |
|--|---|--|---|
| | 1 month after booster dose (n ^b =67) | 1 month after dose 2 (n ^b =96) | |
| | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils)

consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

18 months when stored at -90 °C to -60 °C.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 18-month shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, and within the 10-week storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1.3 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and an orange flip-off plastic cap with aluminium seal. Each vial contains 10 doses, see section 6.6.

Pack size: 10 vials

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- Verify that the vial has an **orange plastic cap** and the product **name is Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty JN.1 for children aged 5 to 11 years.
Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/034

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty JN.1 10 micrograms/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial with a blue cap. Do not dilute prior to use.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

One dose (0.3 mL) contains 10 micrograms of bretovameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Bretovameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron JN.1).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

The vaccine is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty JN.1 10 micrograms/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)

Comirnaty JN.1 10 micrograms/dose dispersion for injection is administered intramuscularly as a single dose of 0.3 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Comirnaty JN.1 10 micrograms/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty JN.1 10 micrograms/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

Single dose vials

Single dose vials of Comirnaty JN.1 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty JN.1.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty JN.1 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty JN.1 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty JN.1 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty JN.1 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty JN.1 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty JN.1 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty JN.1 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty JN.1 can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty JN.1 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty JN.1 is inferred from safety data of the prior Comirnaty vaccine.

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of the initially approved Comirnaty vaccine 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of

age that received 2 doses were injection site pain (> 80%), fatigue (> 50%), headache (> 30%), injection site redness and swelling (\geq 20%), myalgia, chills, and diarrhoea (> 10%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain (> 60%), fatigue (> 30%), headache (> 20%), myalgia, chills, injection site redness and swelling (> 10%).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for \geq 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for \geq 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 40%), chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for \geq 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Omicron-adapted Comirnaty

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain ($> 60\%$), fatigue ($> 40\%$), headache ($> 20\%$), and muscle pain ($> 10\%$).

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 mcg) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain ($> 60\%$), fatigue ($> 50\%$), headache ($> 40\%$), muscle pain ($> 20\%$), chills ($> 10\%$), and joint pain ($> 10\%$).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 5 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 5 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ⁱ |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 2.

Table 2. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Vaccine Group (as Assigned/Randomized) | | | | |
|--|----------------------------------|---|---|--|---|---|
| | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4 | | Study 3 Comirnaty 10 mcg Dose 3 and 1 Month After Dose 3 | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg |
| | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| Omicron BA.4-5 - NT50 (titre) ^e | Pre-vaccination | 102 | 488.3 (361.9, 658.8) | 112 | 248.3 (187.2, 329.5) | - |
| | 1 month | 102 | 2 189.9 (1 742.8, 2 751.7) | 113 | 1 393.6 (1 175.8, 1 651.7) | 1.12 (0.92, 1.37) |
| Reference strain - NT50 (titre) ^e | Pre-vaccination | 102 | 2 904.0 (2 372.6, 3 554.5) | 113 | 1 323.1 (1 055.7, 1 658.2) | - |
| | 1 month | 102 | 8 245.9 (7 108.9, 9 564.9) | 113 | 7 235.1 (6 331.5, 8 267.8) | - |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 through 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 4).

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | | |
|---|--|---|----------------------------|---|-----------------------------|---|--|--|-----------------------------------|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison | |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty | |
| | n ^a | GMT ^c (95% CI ^c) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^c) | GMR ^c (95% CI ^c) | |
| | Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g | |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | | |
| SARS-CoV-2 neutralization assay | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison | |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty | |
| | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) | |
| | Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥ 4 × LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

- e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 4. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference Strain – NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n^{1b} Surveillance time^c (n^{2d}) | Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d}) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N^a=20 998 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=21 096 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI^e) |
|-------------------------------|---|---|--|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.

- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI^c) |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- a. n1 = Number of participants meeting the endpoint definition.
- b. n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 8. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 9.

Table 9. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 10.

Table 10. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| Assay | Sampling time point ^a | | 1 month after booster dose/ 1 month after dose 2 |
|--|---|--|---|
| | 1 month after booster dose (n ^b =67) | 1 month after dose 2 (n ^b =96) | |
| | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils)

consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

18 months when stored at -90 °C to -60 °C.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

Single dose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 18-month shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, within the 10-week storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Opened vials

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

Comirnaty JN.1 dispersion is supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a blue flip-off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

Single dose vials pack size: 10 vials.

Multidose vials pack size: 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **blue plastic cap** and the product **name is Comirnaty JN.1 10 micrograms/dose dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty JN.1 for children aged 5 to 11 years.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/032

Multidose vials

EU/1/20/1528/033

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

| Container | Doses per container (see sections 4.2 and 6.6) | Content per dose |
|--|---|--|
| Multidose vial (0.4 mL) (maroon cap) | 10 doses of 0.2 mL after dilution | One dose (0.2 mL) contains 3 micrograms of bretovameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles). |
| Multidose vial (0.48 mL) (yellow cap) | 3 doses of 0.3 mL after dilution | One dose (0.3 mL) contains 3 micrograms of bretovameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles). |

Bretovameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron JN.1).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in infants and children aged 6 months to 4 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Infants and children 6 months to 4 years of age without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty JN.1 3 micrograms/dose is administered intramuscularly after dilution as a primary course of 3 doses. It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 and 5.1).

If a child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty JN.1 3 micrograms/dose is administered intramuscularly after dilution as a single dose for infants and children 6 months to 4 years of age.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 6 months to 4 years

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Interchangeability

The primary course may consist of any previous or current Comirnaty vaccine but not exceeding the total number of doses required as primary course. The primary course should only be administered once.

The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers has not been established.

Paediatric population

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

Maroon cap (10-dose vial)

After dilution, vials with a **maroon cap** of Comirnaty JN.1 contain **10 doses of 0.2 mL** of vaccine. In order to extract 10 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain **0.2 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.2 mL**, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Yellow cap (3-dose vial)

After dilution, vials with a **yellow cap** of Comirnaty JN.1 contain **3 doses of 0.3 mL** of vaccine. Standard syringes and needles can be used to extract 3 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

In infants from 6 to less than 12 months of age, the recommended injection site is the anterolateral aspect of the thigh. In individuals 1 year of age and older, the recommended injection site is the anterolateral aspect of the thigh or the deltoid muscle.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty JN.1 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty JN.1 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty JN.1 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Summary of Product Characteristics for those formulations.

4.7 Effects on ability to drive and use machines

Comirnaty JN.1 has no or negligible influence on the ability to drive, cycle, and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive, cycle, or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty JN.1 is inferred from safety data of the prior Comirnaty vaccines.

Comirnaty

Infants 6 to 23 months of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 2 176 infants (1 458 initially approved Comirnaty 3 mcg and 718 placebo) were 6 to 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 720 infants 6 to 23 months of age who received a 3-dose primary course (483 Comirnaty 3 mcg and 237 placebo) have been followed for a median of 1.7 months after the third dose.

The most frequent adverse reactions in infants 6 to 23 months of age that received any primary course dose included irritability (> 60%), drowsiness (> 40%), decreased appetite (> 30%), tenderness at the injection site (> 20%), injection site redness and fever (> 10%).

Children 2 to 4 years of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 3 541 children (2 368 Comirnaty 3 mcg and 1 173 placebo) were 2 to 4 years of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 1 268 children 2 to 4 years of age who received a 3-dose primary course (863 Comirnaty 3 mcg and 405 placebo) have been followed a median of 2.2 months after the third dose.

The most frequent adverse reactions in children 2 to 4 years of age that received any primary course dose included pain at injection site and fatigue (> 40%), injection site redness and fever (> 10%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of Comirnaty 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain (> 80%), fatigue (> 50%), headache (> 30%), injection site redness and swelling ($\geq 20\%$), myalgia, chills and diarrhoea (> 10%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain (> 60%), fatigue (> 30%), headache (> 20%), myalgia, chills, injection site redness and swelling (> 10%).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills ($> 30\%$), arthralgia ($> 20\%$), pyrexia and injection site swelling ($> 10\%$) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia ($> 30\%$), chills and arthralgia ($> 20\%$).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Omicron-adapted Comirnaty

Infants 6 to 23 months of age – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 39 participants 6 to 23 months of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg)

2.1 to 8.6 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.7 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reaction in participants 6 to 23 months of age was irritability (> 20%), decreased appetite (> 10%), and drowsiness (> 10%).

Children 2 to 4 years of age – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 124 participants 2 to 4 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.2 to 8.6 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.8 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 2 to 4 years of age were injection site pain (> 30%) and fatigue (> 20%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain (> 60%), fatigue (> 40%), headache (> 20%), and muscle pain (> 10%).

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 micrograms) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain (> 60%), fatigue (> 50%), headache (> 40%), muscle pain (> 20%), chills (> 10%), and joint pain (> 10%).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 6 months of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 6 months of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash ⁱ , pruritus, urticaria, angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite ^j |
| Psychiatric disorders | Very common | Irritability ^k |
| | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache; drowsiness ^k |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ^l |
| General disorders and administration site conditions | Very common | Injection site pain; injection site tenderness ^k ; fatigue; chills; pyrexia ^f ; Injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in participants 6 months to 11 years of age.
- The frequency category for rash was common in participants 6 to 23 months of age.
- The frequency category for decreased appetite was very common in participants 6 to 23 months of age.
- Irritability, injection site tenderness, and drowsiness pertain to participants 6 to 23 months of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in infants and children 6 months to 4 years of age – after the booster (fourth dose)

In an analysis of a subset from Study 6, 60 participants 6 months to 4 years of age received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) after receiving 3 prior doses of Comirnaty 3 micrograms dose concentrate for dispersion. Results include immunogenicity data from a comparator subset of participants 6 months to 4 years of age in Study 3 who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion.

At 1 month after a booster dose (fourth dose), a booster dose with Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) elicited higher Omicron BA.4-5 specific neutralizing titres (regardless of baseline SARS-CoV-2 status) compared with the titres in the comparator group who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion. Comirnaty Original/Omicron BA.4-5

(1.5/1.5 mcg) also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 6 months to 4 years of age are presented in Table 2.

Table 2. Geometric mean titres – Study 6 subset – participants with or without evidence of infection – 6 months through 4 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Age group | Sampling time point ^a | Vaccine group (as assigned/randomized) | | | |
|--|--------------------------|----------------------------------|--|--|--|--|
| | | | Study 6 Comirnaty Original/Omicron BA.4-5 1.5/1.5 mcg Dose 4 and 1 month after Dose 4 | | Study 3 Comirnaty 3 mcg Dose 3 and 1 month after Dose 3 | |
| | | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) |
| Omicron BA.4-5 - NT50 (titre) ^d | 6 months through 4 years | Pre-vaccination | 54 | 192.5 (120.4, 307.8) | 54 | 70.5 (51.1, 97.2) |
| | | 1 month | 58 | 1 695.2 (1 151.8, 2 494.9) | 54 | 607.9 (431.1, 857.2) |
| Reference strain - NT50 (titre) ^d | 6 months through 4 years | Pre-vaccination | 57 | 2 678.1 (1 913.0, 3 749.2) | 53 | 776.8 (536.4, 1 125.0) |
| | | 1 month | 58 | 9 733.0 (7 708.2, 12 289.6) | 53 | 9 057.3 (7 223.4, 11 356.8) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Protocol-specified timing for blood sample collection.

b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.

c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.

d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 3.

Table 3. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Vaccine group (as assigned/randomized) | | | | |
|--|----------------------------------|---|---|--|---|---|
| | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 month after Dose 4 | | Study 3 Comirnaty 10 mcg Dose 3 and 1 month after Dose 3 | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | GMR ^d (95% CI ^d) |
| Omicron BA.4-5 - NT50 (titre) ^e | Pre-vaccination | 102 | 488.3 (361.9, 658.8) | 112 | 248.3 (187.2, 329.5) | - |
| | 1 month | 102 | 2 189.9 (1 742.8, 2 751.7) | 113 | 1 393.6 (1 175.8, 1 651.7) | 1.12 (0.92, 1.37) |
| Reference strain - NT50 (titre) ^e | Pre-vaccination | 102 | 2 904.0 (2 372.6, 3 554.5) | 113 | 1 323.1 (1 055.7, 1 658.2) | - |
| | 1 month | 102 | 8 245.9 (7 108.9, 9 564.9) | 113 | 7 235.1 (6 331.5, 8 267.8) | - |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 to 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 4).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 4).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 5).

Table 4. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | |
|---|---|---|---------------------------|---|-----------------------------|---|--|--|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | n ^a | GMT ^c (95% CI ^e) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^c) | GMR ^c (95% CI ^c) |
| Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | |
| SARS-CoV-2 neutralization assay | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) |
| Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥ 4 × LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 5. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference strain - NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n^{1b} Surveillance time^c (n^{2d}) | Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d}) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 7.

Table 7. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N ^a =20 998 Cases n1 ^b Surveillance time ^c (n2 ^d) | Placebo N ^a =21 096 Cases n1 ^b Surveillance time ^c (n2 ^d) | Vaccine efficacy % (95% CI ^e) |
|-------------------------------|---|---|---|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.

- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 8) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 8. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI)^c |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- a. n1 = Number of participants meeting the endpoint definition.
- b. n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 9. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 9. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 10.

Table 10. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 11.

Table 11. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| Assay | Sampling time point ^a | | 1 month after booster dose/ 1 month after dose 2 GMR ^d (95% CI ^d) |
|--|---|---|---|
| | 1 month after booster dose (n ^b =67) GMT ^c (95% CI ^c) | 1 month after dose 2 (n ^b =96) GMT ^c (95% CI ^c) | |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Efficacy and immunogenicity of a 3-dose primary course in infants and children 6 months to 4 years of age

The efficacy analysis of Study 3 was performed across the combined population of participants 6 months through 4 years of age based on cases confirmed among 873 participants in the COVID-19 mRNA Vaccine group and 381 participants in the placebo group (2:1 randomization ratio) who received all 3 doses of study intervention during the blinded follow-up period when the Omicron variant of SARS-CoV-2 (BA.2) was the predominant variant in circulation (data cut-off date of 17 June 2022).

The vaccine efficacy results after Dose 3 in participants 6 months through 4 years of age are presented in Table 12.

Table 12. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Phase 2/3 – 6 Months to 4 Years of Age – Evaluable Efficacy (3-Dose) Population

| First COVID-19 occurrence from 7 days after Dose 3 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|--|--|
| Subgroup | COVID-19 mRNA Vaccine 3 mcg/Dose N^a=873 Cases n¹^b Surveillance Time^c (n²^d) | Placebo N^a=381 Cases n¹^b Surveillance Time^c (n²^d) | Vaccine Efficacy % (95% CI)^e |
| 6 months through 4 years ^e | 13 0.124 (794) | 21 0.054 (351) | 73.2 (43.8, 87.6) |
| 2 through 4 years | 9 0.081 (498) | 13 0.033 (204) | 71.8 (28.6, 89.4) |
| 6 months through 23 months | 4 0.042 (296) | 8 0.020 (147) | 75.8 (9.7, 94.7) |

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (i.e. negative N-binding antibody [serum] result at Dose 1, 1 month post-Dose 2 (if available), Dose 3 (if available) visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 3) and had no medical history of COVID-19 were included in the analysis.

- N = number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 3 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Vaccine efficacy in participants with or without prior SARS-CoV-2 infection was similar to those participants without prior SARS-CoV-2 infection.

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 12 cases (8 COVID-19 mRNA Vaccine and 4 placebo) among participants 6 months to 4 years of age. Among participants 6 months through 23 months of age, severe COVID-19 criteria were fulfilled for 3 cases (2 COVID-19 mRNA Vaccine and 1 placebo).

Immunogenicity analyses have been performed in the immunobridging subset of 82 Study 3 participants 6 to 23 months of age and 143 Study 3 participants 2 to 4 years of age without evidence of infection up to 1 month after Dose 3 based on a data cut-off date of 29 April 2022.

SARS-CoV-2 50% neutralising antibody titres (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 6 to 23 months of age and 2 to 4 years of age from Study 3 at 1 month after the 3-dose primary course and a randomly selected subset from Study 2 Phase 2/3 participants 16 to 25 years of age at 1 month after the 2-dose primary course, using a microneutralisation assay against the reference strain (USA_WA1/2020).

The primary immunobridging analyses compared the geometric mean titres (using a geometric mean ratio [GMR]) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 to 23 months of age and 2 to 4 years of age and up to 1 month after Dose 2 in participants 16 to 25 years of age. The

prespecified immunobridging criteria were met for both the GMR and the seroresponse difference for both age groups (Table 13).

Table 13. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset - participants 6 months to 4 years of age (Study 3) 1 month after Dose 3 and participants 16 to 25 years of age (Study 2) 1 month after Dose 2 – without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | |
|---|----------------|---|-----------------------------|----------------|---|--|--|
| SARS-CoV-2 neutralization assay - NT50 (titre) ^e | | | | | | | |
| Age | N ^a | GMT ^b (95% CI ^b) (1 month after Dose 3) | Age | N ^a | GMT ^b (95% CI ^b) (1 month after Dose 2) | Age | GMR ^{c,d} (95% CI) |
| 2 to 4 years | 143 | 1 535.2 (1 388.2, 1 697.8) | 16 to 25 years of age | 170 | 1 180.0 (1 066.6, 1 305.4) | 2 to 4 years/16 to 25 years of age | 1.30 (1.13, 1.50) |
| 6 to 23 months | 82 | 1 406.5 (1 211.3, 1 633.1) | 16 to 25 years of age | 170 | 1 180.0 (1 066.6, 1 305.4) | 6 to 23 months years/16 to 25 years of age | 1.19 (1.00, 1.42) |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | |
| SARS-CoV-2 neutralization assay - NT50 (titre) ^e | | | | | | | |
| Age | N ^a | n ^f (%) (95% CI ^g) (1 month after Dose 3) | Age | N ^a | n ^f (%) (95% CI ^g) (1 month after Dose 2) | Age | Difference in seroresponse rates % ^h (95% CI) ^j |
| 2 to 4 years | 141 | 141(100.0) (97.4, 100.0) | 16 to 25 years of age | 170 | 168 (98.8) (95.8, 99.9) | 2 to 4 years/16 to 25 years of age | 1.2 (1.5, 4.2) |
| 6 to 23 months | 80 | 80 (100.0) (95.5, 100.0) | 16 to 25 years of age | 170 | 168 (98.8) (95.8, 99.9) | 6 to 23 months years/16 to 25 years of age | 1.2 (3.4, 4.2) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [(i.e. N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point for GMTs and number of participants with valid and determinate assay results for the specified assay at both baseline and the given dose/sampling time point for seroresponse rates.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.

- c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (younger age group minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- d. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on GMR is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- f. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
- g. Exact 2-sided CI based on the Clopper and Pearson method.
- h. Difference in proportions, expressed as a percentage (younger age group minus 16 to 25 years of age).
- i. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- j. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

18 months when stored at -90 °C to -60 °C.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 18-month shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, and within the 10 weeks storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Maroon cap (10-dose vial)

0.4 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a **maroon flip-off plastic cap** with aluminium seal. Each vial contains **10 doses**, see section 6.6.

Pack size: 10 vials

Yellow cap (3-dose vial)

0.48 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a **yellow flip-off plastic cap** with aluminium seal. Each vial contains **3 doses**, see section 6.6.

Pack size: 10 vials

6.6 Special precautions for disposal and other handling

Maroon cap (10-dose vial)

Handling instructions prior to use for a vial with a maroon cap

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label or a different cap colour, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.

- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution for a vial with a maroon cap

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses using a vial with a maroon cap

- After dilution, the vial contains 2.6 mL from which **10 doses of 0.2 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw **0.2 mL** of Comirnaty JN.1 for infants and children aged 6 months to 4 years. **Low dead-volume syringes and/or needles** should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain **0.2 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.2 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Yellow cap (3-dose vial)

Handling instructions prior to use for a vial with a yellow cap

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **yellow plastic cap** and the product **name is Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label, or a different cap colour, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution for a vial with a yellow cap

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.1 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.1 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.3 mL doses using a vial with a yellow cap

- After dilution, the vial contains 1.58 mL from which **3 doses** of **0.3 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw **0.3 mL** of Comirnaty JN.1 for infants and children aged 6 months to 4 years. **Standard syringes and/or needles** can be used in order to extract 3 doses from a single vial.
- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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55131 Mainz
Germany
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Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

Maroon cap (10-dose vial)

EU/1/20/1528/036

Yellow cap (3-dose vial)

EU/1/20/1528/035

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty KP.2 30 micrograms/dose dispersion for injection
 Comirnaty KP.2 30 micrograms/dose dispersion for injection in pre-filled syringe
 COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial, or a single dose pre-filled syringe. The single dose vial and multidose vial have a grey cap. Do not dilute prior to use.

Table 1. Comirnaty KP.2 30 micrograms/dose qualitative and quantitative composition

| Product presentation | Container | Dose(s) per container (see sections 4.2 and 6.6) | Contents per dose |
|---|-----------------------------|---|--|
| Comirnaty KP.2 30 micrograms/dose dispersion for injection | Single dose vial | 1 dose of 0.3 mL | One dose (0.3 mL) contains 30 micrograms of mRNA encoding KP.2, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles). |
| | Multidose vial (2.25 mL) | 6 doses of 0.3 mL | |
| Comirnaty KP.2 30 micrograms/dose dispersion for injection in pre-filled syringe | Pre-filled syringe | 1 dose of 0.3 mL | |

The mRNA encoding KP.2 is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron KP.2).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.
 The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty KP.2 30 micrograms/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older

Comirnaty KP.2 30 micrograms/dose is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty KP.2 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 12 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Paediatric population

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Elderly population

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty KP.2 30 micrograms/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

Single dose vials

Single dose vials of Comirnaty KP.2 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty KP.2.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty KP.2 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.

- Do not pool excess vaccine from multiple vials.

Pre-filled syringes

- Each single dose pre-filled syringe of Comirnaty KP.2 contains 1 dose of 0.3 mL of vaccine.
- Attach a needle appropriate for intramuscular injection and administer the entire volume.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty KP.2 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty KP.2 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

Comirnaty KP.2 may be administered concomitantly with seasonal influenza vaccine.

Different injectable vaccines should be given at different injection sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty KP.2 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty KP.2 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty KP.2 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty KP.2 can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty KP.2 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty KP.2 is inferred from safety data of the prior Comirnaty vaccines.

Comirnaty 30 mcg

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of the initially approved Comirnaty vaccine and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills ($> 30\%$), arthralgia ($> 20\%$), pyrexia and injection site swelling ($> 10\%$) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia ($> 30\%$), chills and arthralgia ($> 20\%$).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Participants 12 years of age and older – after subsequent booster doses

The safety of a booster dose of Comirnaty in participants 12 years of age and older is inferred from safety data from studies of a booster dose of Comirnaty in participants 18 years of age and older.

A subset of 325 adults 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 90 to 180 days after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of 1.4 months up to a data cut-off date of 11 March 2022. The most frequent adverse reactions in these participants were injection site pain ($> 70\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia and chills ($> 20\%$), and arthralgia ($> 10\%$).

In a subset from Study 4 (Phase 3), 305 adults > 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 5 to 12 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of at least 1.7 months up to a data cut-off date of 16 May 2022. The overall safety profile for the Comirnaty booster (fourth dose) was similar to that seen after the Comirnaty booster (third dose). The most frequent adverse reactions in participants > 55 years of age were injection site pain ($> 60\%$), fatigue ($> 40\%$), headache ($> 20\%$), myalgia and chills ($> 10\%$).

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified (see section 5.1).

Omicron-adapted Comirnaty

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 micrograms) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain ($> 60\%$), fatigue ($> 50\%$), headache ($> 40\%$), muscle pain ($> 20\%$), chills ($> 10\%$), and joint pain ($> 10\%$).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 2. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 12 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ^h |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Most cases appeared to be non-serious and temporary in nature.

Safety with concomitant vaccine administration

In Study 8, a Phase 3 study, participants 18 through 64 years of age who received Comirnaty coadministered with seasonal inactivated influenza vaccine (SIIV), quadrivalent followed 1 month

later by placebo, were compared to participants who received an inactivated influenza vaccine with placebo followed 1 month later by Comirnaty alone (n= 553 to 564 participants in each group). Reactogenicity events were reported more frequently by participants who received Comirnaty coadministered with SIIV, quadrivalent, compared to participants who received Comirnaty alone, but overall the reactogenicity events were mostly mild to moderate in severity. The most common adverse reactions reported in the coadministration group and after Comirnaty alone were injection site pain (86.2% and 84.4%, respectively), fatigue (64.0% and 50.8%, respectively) and headache (47.2% and 37.8%, respectively).

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 to 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 to 17 years of age, 18 to 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 to 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 to 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 4).

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | |
|--|---|---|---------------------------|---|-----------------------------|---|--|--|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | n ^a | GMT ^c (95% CI ^e) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^e) | GMR ^c (95% CI ^e) |
| Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g |

| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | |
|---|-----------------------------------|---|---------------------------|---|-----------------------------|---|---|---|
| | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison ≥ 56 years of age |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| SARS-CoV-2 neutralization assay | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) |
| Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage.
- 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 4. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|--|----------------------------|--|---------------------------|--|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI) ^c | n ^b | GMT ^c (95% CI) ^c | n ^b | GMT ^c (95% CI) ^c |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference Strain – NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty 30 mcg

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n^{1b} Surveillance time^c (n^{2d}) | Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d}) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N^a=20 998 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=21 096 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI^e) |
|-------------------------------|---|---|--|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI^c) |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.

f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.

g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without

evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Immunogenicity in participants 18 years of age and older – after booster dose

Effectiveness of a booster dose of Comirnaty was based on an assessment of 50% neutralizing antibody titres (NT50) against SARS-CoV-2 (USA_WA1/2020) in Study 2. In this study, the booster dose was administered 5 to 8 months (median 7 months) after the second dose. In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4-fold rise in NT50 from baseline (before primary series). These analyses are summarized in Table 8.

Table 8. SARS-CoV-2 neutralization assay - NT50 (titre)[†] (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 through 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population[‡]

| | n | 1 month after booster dose (95% CI) | 1 month after primary series (95% CI) | 1 month after booster dose - 1 month after primary series (97.5% CI) | Met noninferiority objective (Y/N) |
|---|------------------|--|---|--|------------------------------------|
| Geometric mean 50% neutralizing titre (GMT)^b | 212 ^a | 2 466.0 ^b (2 202.6, 2 760.8) | 755.7 ^b (663.1, 861.2) | 3.26 ^c (2.76, 3.86) | Y ^d |
| Seroresponse rate (%) for 50% neutralizing titre[†] | 200 ^e | 199 ^f 99.5% (97.2%, 100.0%) | 190 ^f 95.0% (91.0%, 97.6%) | 4.5% ^g (1.0%, 7.9% ^h) | Y ⁱ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

- † SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.
- * Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of Comirnaty) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.
- ± All eligible participants who had received 2 doses of Comirnaty as initially randomised, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Comirnaty, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.
 - a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
 - b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
 - c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
 - d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80 .
 - e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
 - f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.
 - g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
 - h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
 - i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.

Relative vaccine efficacy in participants 16 years of age and older – after booster dose

An interim efficacy analysis of Study 4, a placebo-controlled booster study performed in approximately 10 000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up. The booster dose was administered 5 to 13 months (median 11 months) after the second dose. Vaccine efficacy of the Comirnaty booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed.

The relative vaccine efficacy information for participants 16 years of age and older without prior evidence of SARS-CoV-2 infection is presented in Table 9. Relative vaccine efficacy in participants with or without evidence of prior SARS-CoV-2 infection was 94.6% (95% confidence interval of 88.5% to 97.9%), similar to that seen in those participants without evidence of prior infection. Primary COVID-19 cases observed from 7 days after booster vaccination were 7 primary cases in the Comirnaty group, and 124 primary cases in the placebo group.

Table 9. Vaccine efficacy – First COVID-19 occurrence from 7 days after booster vaccination – participants 16 years of age and older without evidence of infection – evaluable efficacy population

| First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|--|--|---|
| | Comirnaty N^a=4 695 Cases n1^b Surveillance Time^c (n2^d) | Placebo N^a=4 671 Cases n1^b Surveillance Time^c (n2^d) | Relative Vaccine Efficacy^e % (95% CI^f) |
| First COVID-19 occurrence from 7 days after booster vaccination | 6 0.823 (4 659) | 123 0.792 (4 614) | 95.3 (89.5, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non-booster).
- Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Immunogenicity of a booster dose following primary vaccination with another authorised COVID-19 vaccine

Effectiveness of a Comirnaty booster dose (30 mcg) in individuals who completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose) is inferred from immunogenicity data from an independent National Institutes of Health (NIH) study phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States. In this study, adults (range 19 to 80 years of age) who had completed primary vaccination with Moderna 100 mcg 2-dose series (N = 51, mean age 54±17), Janssen single dose (N = 53, mean age 48±14), or Comirnaty 30 mcg 2-dose series (N = 50, mean age 50±18) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection received a booster dose of Comirnaty (30 mcg). The boost with Comirnaty induced a 36, 12, and 20 GMR-fold rise in neutralising titres following the Janssen, Moderna, and Comirnaty primary doses, respectively.

Heterologous boosting with Comirnaty was also evaluated in the CoV-BOOST study (EudraCT 2021-002175-19), a multicentre, randomised, controlled, phase 2 trial of third dose booster vaccination against COVID-19, in which 107 adult participants (median age 71 years of age, interquartile range 54 to 77 years of age) were randomised at least 70 days post 2 doses of AstraZeneca COVID-19 Vaccine. After the AstraZeneca COVID-19 Vaccine primary series, pseudovirus (wild-type), neutralising antibody NT50 GMR-fold change increased 21.6-fold with heterologous Comirnaty booster (n = 95).

Immunogenicity in participants > 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)

In an interim analysis of a subset from Study 4 (Substudy E), 305 participants > 55 years of age who had completed a series of 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 5 to 12 months after receiving Dose 3. For the Immunogenicity subset data see Table 7.

Immunogenicity in participants 18 to ≤ 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 325 participants 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 90 to 180 days after receiving Dose 3. For the Immunogenicity subset data see Table 10.

Table 10. Summary of immunogenicity data from participants in C4591031 Substudy D (cohort 2 full expanded set) and Substudy E (expanded cohort immunogenicity subset) who received Comirnaty 30 mcg as booster (fourth dose) – participants without evidence of infection up to 1 month after booster dose – evaluable immunogenicity population

| | Dose/ sampling time point ^a | Substudy D (18 to ≤ 55 years of age) Comirnaty 30 mcg | | Substudy E (> 55 years of age) Comirnaty 30 mcg | |
|--|--|---|--|---|--|
| | | N ^b | GMT (95% CI ^d) | N ^b | GMT (95% CI ^d) |
| GMT | | | | | |
| SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre) | 1/Prevax | 226 | 315.0 (269.0, 368.9) | 167 | 67.5 (52.9, 86.3) |
| | 1/1 Month | 228 | 1 063.2 (935.8, 1 207.9) | 163 | 455.8 (365.9, 567.6) |
| SARS-CoV-2 neutralization assay – reference strain – NT50 (titre) | 1/Prevax | 226 | 3 999.0 (3 529.5, 4 531.0) | 179 | 1 389.1 (1 142.1, 1 689.5) |
| | 1/1 Month | 227 | 12 009.9 (10 744.3, 13 424.6) | 182 | 5 998.1 (5 223.6, 6 887.4) |
| Seroresponse rate at 1 month post-Dose 4 | | N ^c | n ^e (%) (95% CI ^f) | N ^c | n ^e (%) (95% CI ^f) |
| SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre) | 1/1 Month | 226 | 91 (40.3%) (33.8, 47.0) | 149 | 85 (57.0%) (48.7, 65.1) |
| SARS-CoV-2 neutralization assay – reference strain – NT50 (titre) | 1/1 Month | 225 | 76 (33.8%) (27.6, 40.4) | 179 | 88 (49.2%) (41.6, 56.7) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Median time from Dose 3 to Dose 4 of Comirnaty 30 mcg is 4.0 months for Substudy D Cohort 2 and 6.3 months for Substudy E expanded cohort.

Note: Substudy D Full Expanded Set = Cohort 2 excluding the sentinel group; Substudy E Immunogenicity Subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving ≥ 4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the post-vaccination measure of ≥ 4 × LLOQ is considered a seroresponse.

a. Protocol-specified timing for blood sample collection.

b. N = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.

c. N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.

d. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

- e. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- f. Exact 2-sided CI, based on the Clopper and Pearson method.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Vials

Unopened vials

The vaccine will be received frozen at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Frozen vaccine can be stored either at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$ or $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ upon receipt.

18 months when stored at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for up to 10 weeks.

Thawing procedure

Single dose vials

When stored frozen at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$, 10-vial packs of single dose vials of the vaccine can be thawed at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for 2 hours or individual vials can be thawed at room temperature (up to $30\text{ }^{\circ}\text{C}$) for 30 minutes.

Multidose vials

When stored frozen at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$, 10-vial packs of multidose vials of the vaccine can be thawed at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ for 6 hours or individual vials can be thawed at room temperature (up to $30\text{ }^{\circ}\text{C}$) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ within the 18-month shelf life.

- Upon moving the vaccine to $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ it should be stored at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between $8\text{ }^{\circ}\text{C}$ and $30\text{ }^{\circ}\text{C}$.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from $-2\text{ }^{\circ}\text{C}$ to $2\text{ }^{\circ}\text{C}$, within the 10-week storage period between $2\text{ }^{\circ}\text{C}$ and $8\text{ }^{\circ}\text{C}$.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of $8\text{ }^{\circ}\text{C}$ to $30\text{ }^{\circ}\text{C}$, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Opened vials

Chemical and physical in-use stability has been demonstrated for 12 hours at $2\text{ }^{\circ}\text{C}$ to $30\text{ }^{\circ}\text{C}$, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of

opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Glass pre-filled syringes

The vaccine will be received and stored at 2 °C to 8 °C (refrigerated only).
8 months when stored at 2 °C to 8 °C.

Prior to use, pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C and 30 °C and can be handled in room light conditions.

6.4 Special precautions for storage

Vials

Store single dose vials and multidose vials in a freezer at –90 °C to –60 °C.

Glass pre-filled syringes

Store glass pre-filled syringes at 2 °C to 8 °C. DO NOT FREEZE.

Vials and pre-filled syringes

Store the vaccine in the original package in order to protect from light.
During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

Single dose and multidose vials

Supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.
One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

Single dose vials pack size: 10 vials.
Multidose vials pack size: 10 vials.

Not all pack sizes may be marketed.

Glass pre-filled syringes

Supplied in a single dose glass pre-filled syringe (type I glass syringe) with plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber) without needle.

Pack size: 10 pre-filled syringes.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty KP.2 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

Instructions applicable to single dose and multidose vials

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty KP.2 30 micrograms/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty KP.2.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the multidose vial. Discard any unused vaccine 12 hours after first puncture.

Instructions applicable to glass pre-filled syringes

- Prior to use, pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.
- Remove tip cap by slowly turning the cap counterclockwise. Do not shake. Attach a needle appropriate for intramuscular injection and administer the entire volume.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/037

Multidose vials

EU/1/20/1528/038

Glass pre-filled syringes

EU/1/20/1528/039

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty KP.2 10 micrograms/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial with a blue cap. Do not dilute prior to use.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

One dose (0.3 mL) contains 10 micrograms of mRNA encoding KP.2, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

The mRNA encoding KP.2 is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron KP.2).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

The vaccine is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty KP.2 10 micrograms/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)

Comirnaty KP.2 10 micrograms/dose dispersion for injection is administered intramuscularly as a single dose of 0.3 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty KP.2 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Comirnaty KP.2 10 micrograms/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty KP.2 10 micrograms/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

Single dose vials

Single dose vials of Comirnaty KP.2 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty KP.2.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty KP.2 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty KP.2 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty KP.2 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty KP.2 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty KP.2 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty KP.2 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty KP.2 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty KP.2 can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty KP.2 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty KP.2 is inferred from safety data of the prior Comirnaty vaccine.

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of the initially approved Comirnaty vaccine 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of

age that received 2 doses were injection site pain (> 80%), fatigue (> 50%), headache (> 30%), injection site redness and swelling (\geq 20%), myalgia, chills, and diarrhoea (> 10%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain (> 60%), fatigue (> 30%), headache (> 20%), myalgia, chills, injection site redness and swelling (> 10%).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for \geq 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for \geq 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 40%), chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for \geq 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Omicron-adapted Comirnaty

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain ($> 60\%$), fatigue ($> 40\%$), headache ($> 20\%$), and muscle pain ($> 10\%$).

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 mcg) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain ($> 60\%$), fatigue ($> 50\%$), headache ($> 40\%$), muscle pain ($> 20\%$), chills ($> 10\%$), and joint pain ($> 10\%$).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 5 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 5 years of age and older

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash, pruritus, urticaria ^b , angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite |
| Psychiatric disorders | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ⁱ |
| General disorders and administration site conditions | Very common | Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 2.

Table 2. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Vaccine Group (as Assigned/Randomized) | | | | |
|--|----------------------------------|---|---|--|---|---|
| | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4 | | Study 3 Comirnaty 10 mcg Dose 3 and 1 Month After Dose 3 | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg |
| | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| Omicron BA.4-5 - NT50 (titre) ^e | Pre-vaccination | 102 | 488.3 (361.9, 658.8) | 112 | 248.3 (187.2, 329.5) | - |
| | 1 month | 102 | 2 189.9 (1 742.8, 2 751.7) | 113 | 1 393.6 (1 175.8, 1 651.7) | 1.12 (0.92, 1.37) |
| Reference strain - NT50 (titre) ^e | Pre-vaccination | 102 | 2 904.0 (2 372.6, 3 554.5) | 113 | 1 323.1 (1 055.7, 1 658.2) | - |
| | 1 month | 102 | 8 245.9 (7 108.9, 9 564.9) | 113 | 7 235.1 (6 331.5, 8 267.8) | - |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 through 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 4).

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | | |
|---|--|---|----------------------------|---|-----------------------------|---|--|--|-----------------------------------|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison | |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 years of age | ≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty | |
| | n ^a | GMT ^c (95% CI ^c) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^c) | GMR ^c (95% CI ^c) | |
| | Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e | 2.91 (2.45, 3.44) ^f |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g | |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | | |
| SARS-CoV-2 neutralization assay | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison | |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ age ≥ 56 | Comirnaty Original/Omicron BA.4-5 /Comirnaty | |
| | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) | |
| | Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥ 4 × LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

- e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

Table 4. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference Strain – NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n^{1b} Surveillance time^c (n^{2d}) | Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d}) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N^a=20 998 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=21 096 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI^e) |
|-------------------------------|---|---|--|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.

- c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI^c) |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate \geq 30 breaths per minute, heart rate \geq 125 beats per minute, saturation of oxygen \leq 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen $<$ 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure $<$ 90 mm Hg, diastolic blood pressure $<$ 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.

b. n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 8. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=663 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 9.

Table 9. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|---|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre ^f (GMT ^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |
| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
| Seroresponse rate (%) for 50% neutralizing titre ^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 10.

Table 10. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| Assay | Sampling time point ^a | | 1 month after booster dose/ 1 month after dose 2 |
|--|---|--|---|
| | 1 month after booster dose (n ^b =67) | 1 month after dose 2 (n ^b =96) | |
| | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils)

consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

18 months when stored at -90 °C to -60 °C.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

Single dose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 18-month shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, within the 10-week storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Opened vials

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

Comirnaty KP.2 dispersion is supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a blue flip-off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

Single dose vials pack size: 10 vials.

Multidose vials pack size: 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty KP.2 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **blue plastic cap** and the product **name is Comirnaty KP.2 10 micrograms/dose dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty KP.2 for children aged 5 to 11 years.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/040

Multidose vials

EU/1/20/1528/041

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty KP.2 3 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with a yellow cap and must be diluted before use.

One vial (0.48 mL) contains 3 doses of 0.3 mL after dilution, see sections 4.2 and 6.6.

One dose (0.3 mL) contains 3 micrograms of mRNA encoding KP.2, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

The mRNA encoding KP.2 is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron KP.2).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty KP.2 3 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in infants and children aged 6 months to 4 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Infants and children 6 months to 4 years of age without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty KP.2 3 micrograms/dose is administered intramuscularly after dilution as a primary course of 3 doses. It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 and 5.1).

If a child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty KP.2 3 micrograms/dose is administered intramuscularly after dilution as a single dose for infants and children 6 months to 4 years of age.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty KP.2 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 6 months to 4 years

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Interchangeability

The primary course may consist of any previous or current Comirnaty vaccine but not exceeding the total number of doses required as primary course. The primary course should only be administered once.

The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers has not been established.

Paediatric population

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Method of administration

Comirnaty KP.2 3 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials with a **yellow cap** of Comirnaty KP.2 contain **3 doses** of **0.3 mL** of vaccine. Standard syringes and needles can be used to extract 3 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

In infants from 6 to less than 12 months of age, the recommended injection site is the anterolateral aspect of the thigh. In individuals 1 year of age and older, the recommended injection site is the anterolateral aspect of the thigh or the deltoid muscle.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty KP.2 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty KP.2 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty KP.2 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Comirnaty KP.2 3 micrograms/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Summary of Product Characteristics for those formulations.

4.7 Effects on ability to drive and use machines

Comirnaty KP.2 has no or negligible influence on the ability to drive, cycle, and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive, cycle, or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty KP.2 is inferred from safety data of the prior Comirnaty vaccines.

Comirnaty

Infants 6 to 23 months of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 2 176 infants (1 458 initially approved Comirnaty 3 mcg and 718 placebo) were 6 to 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 720 infants 6 to 23 months of age who received a 3-dose primary course (483 Comirnaty 3 mcg and 237 placebo) have been followed for a median of 1.7 months after the third dose.

The most frequent adverse reactions in infants 6 to 23 months of age that received any primary course dose included irritability (> 60%), drowsiness (> 40%), decreased appetite (> 30%), tenderness at the injection site (> 20%), injection site redness and fever (> 10%).

Children 2 to 4 years of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 3 541 children (2 368 Comirnaty 3 mcg and 1 173 placebo) were 2 to 4 years of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 1 268 children 2 to 4 years of age who received a 3-dose primary course (863 Comirnaty 3 mcg and 405 placebo) have been followed a median of 2.2 months after the third dose.

The most frequent adverse reactions in children 2 to 4 years of age that received any primary course dose included pain at injection site and fatigue (> 40%), injection site redness and fever (> 10%).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of Comirnaty 10 mcg and a total of 1 538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 50\%$), headache ($> 30\%$), injection site redness and swelling ($\geq 20\%$), myalgia, chills and diarrhoea ($> 10\%$).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

In a subset from Study 3, a total of 2 408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain ($> 60\%$), fatigue ($> 30\%$), headache ($> 20\%$), myalgia, chills, injection site redness and swelling ($> 10\%$).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 50\%$), myalgia ($> 40\%$), chills ($> 30\%$), arthralgia ($> 20\%$), pyrexia and injection site swelling ($> 10\%$) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Participants 12 years of age and older – after booster dose

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain ($> 80\%$), fatigue ($> 60\%$), headache ($> 40\%$), myalgia ($> 30\%$), chills and arthralgia ($> 20\%$).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

Omicron-adapted Comirnaty

Infants 6 to 23 months of age – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 39 participants 6 to 23 months of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.1 to 8.6 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.7 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reaction in participants 6 to 23 months of age was irritability ($> 20\%$), decreased appetite ($> 10\%$), and drowsiness ($> 10\%$).

Children 2 to 4 years of age – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 124 participants 2 to 4 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.2 to 8.6 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.8 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 2 to 4 years of age were injection site pain ($> 30\%$) and fatigue ($> 20\%$).

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain (> 60%), fatigue (> 40%), headache (> 20%), and muscle pain (> 10%).

Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 micrograms) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain (> 60%), fatigue (> 50%), headache (> 40%), muscle pain (> 20%), chills (> 10%), and joint pain (> 10%).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 6 months of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 6 months of age and older

| System Organ Class | Frequency | Adverse reactions |
|---|-------------|---|
| Blood and lymphatic system disorders | Common | Lymphadenopathy ^a |
| Immune system disorders | Uncommon | Hypersensitivity reactions (e.g. rash ⁱ , pruritus, urticaria, angioedema ^b) |
| | Not known | Anaphylaxis |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite ^j |
| Psychiatric disorders | Very common | Irritability ^k |
| | Uncommon | Insomnia |
| Nervous system disorders | Very common | Headache; drowsiness ^k |
| | Uncommon | Dizziness ^d ; lethargy |
| | Rare | Acute peripheral facial paralysis ^c |
| | Not known | Paraesthesia ^d ; hypoaesthesia ^d |
| Cardiac disorders | Very rare | Myocarditis ^d ; pericarditis ^d |
| Gastrointestinal disorders | Very common | Diarrhoea ^d |
| | Common | Nausea; vomiting ^d |
| Skin and subcutaneous tissue disorder | Uncommon | Hyperhidrosis; night sweats |
| | Not known | Erythema multiforme ^d |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia; myalgia |
| | Uncommon | Pain in extremity ^e |
| Reproductive system and breast disorders | Not known | Heavy menstrual bleeding ^l |

| System Organ Class | Frequency | Adverse reactions |
|--|-------------|---|
| General disorders and administration site conditions | Very common | Injection site pain; injection site tenderness ^k ; fatigue; chills; pyrexia ^f ; Injection site swelling |
| | Common | Injection site redness ^h |
| | Uncommon | Asthenia; malaise; injection site pruritus |
| | Not known | Extensive swelling of vaccinated limb ^d ; facial swelling ^g |

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in participants 6 months to 11 years of age.
- The frequency category for rash was common in participants 6 to 23 months of age.
- The frequency category for decreased appetite was very common in participants 6 to 23 months of age.
- Irritability, injection site tenderness, and drowsiness pertain to participants 6 to 23 months of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Omicron-adapted Comirnaty

Immunogenicity in infants and children 6 months to 4 years of age – after the booster (fourth dose)

In an analysis of a subset from Study 6, 60 participants 6 months to 4 years of age received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) after receiving 3 prior doses of Comirnaty 3 micrograms dose concentrate for dispersion. Results include immunogenicity data from a comparator subset of participants 6 months to 4 years of age in Study 3 who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion.

At 1 month after a booster dose (fourth dose), a booster dose with Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) elicited higher Omicron BA.4-5 specific neutralizing titres (regardless of baseline SARS-CoV-2 status) compared with the titres in the comparator group who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion. Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 6 months to 4 years of age are presented in Table 2.

Table 2. Geometric mean titres – Study 6 subset – participants with or without evidence of infection – 6 months through 4 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Age group | Sampling time point ^a | Vaccine group (as assigned/randomized) | | | |
|--|--------------------------|----------------------------------|--|---|--|---|
| | | | Study 6 Comirnaty Original/Omicron BA.4-5 1.5/1.5 mcg Dose 4 and 1 month after Dose 4 | | Study 3 Comirnaty 3 mcg Dose 3 and 1 month after Dose 3 | |
| | | | n ^b | GMT ^c (95% CI) ^c | n ^b | GMT ^c (95% CI) ^c |
| Omicron BA.4-5 - NT50 (titre) ^d | 6 months through 4 years | Pre-vaccination | 54 | 192.5 (120.4, 307.8) | 54 | 70.5 (51.1, 97.2) |
| | | 1 month | 58 | 1 695.2 (1 151.8, 2 494.9) | 54 | 607.9 (431.1, 857.2) |
| Reference strain - NT50 (titre) ^d | 6 months through 4 years | Pre-vaccination | 57 | 2 678.1 (1 913.0, 3 749.2) | 53 | 776.8 (536.4, 1 125.0) |
| | | 1 month | 58 | 9 733.0 (7 708.2, 12 289.6) | 53 | 9 057.3 (7 223.4, 11 356.8) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 3.

Table 3. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Vaccine group (as assigned/randomized) | | | | |
|--|----------------------------------|---|---|--|---|---|
| | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 month after Dose 4 | | Study 3 Comirnaty 10 mcg Dose 3 and 1 month after Dose 3 | | Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg |
| | | n ^b | GMT ^c (95% CI ^e) | n ^b | GMT ^c (95% CI ^e) | GMR ^d (95% CI ^d) |
| Omicron BA.4-5 - NT50 (titre) ^e | Pre-vaccination | 102 | 488.3 (361.9, 658.8) | 112 | 248.3 (187.2, 329.5) | - |
| | 1 month | 102 | 2 189.9 (1 742.8, 2 751.7) | 113 | 1 393.6 (1 175.8, 1 651.7) | 1.12 (0.92, 1.37) |
| Reference strain - NT50 (titre) ^e | Pre-vaccination | 102 | 2 904.0 (2 372.6, 3 554.5) | 113 | 1 323.1 (1 055.7, 1 658.2) | - |
| | 1 month | 102 | 8 245.9 (7 108.9, 9 564.9) | 113 | 7 235.1 (6 331.5, 8 267.8) | - |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.

- d. GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 to 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 4).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 4).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 5).

Table 4. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | | |
|--|--|---|----------------------------|---|-----------------------------|---|--|--|
| SARS-CoV-2 neutralization assay | Study 5 Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age ≥ 56 years of age | Comirnaty Original/Omicron BA.4-5 /Comirnaty |
| | n ^a | GMT ^c (95% CI ^c) | n ^a | GMT ^b (95% CI ^b) | n ^a | GMT ^b (95% CI ^b) | GMR ^c (95% CI ^c) | GMR ^c (95% CI ^c) |
| | Omicron BA.4-5 - NT50 (titre) ^d | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16) ^e |
| Reference Strain – NT50 (titre) ^d | - | - | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | - | 1.38 (1.22, 1.56) ^g |

| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | | |
|---|--------------------------------------|--|------------------------------|--|--------------------------------|--|--|--|
| | Comirnaty Original/Omicron BA.4-5 | | | | Subset of Study 4 Comirnaty | | Age group comparison | Vaccine group comparison ≥ 56 years of age |
| | 18 through 55 years of age | | 56 years of age and older | | 56 years of age and older | | Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 | Comirnaty Original/ Omicron BA.4-5 /Comirnaty |
| SARS-CoV-2 neutralization assay | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^k) | N ^h | n ⁱ (%) (95% CI ^l) | Difference ^k (95% CI ^l) | Difference ^k (95% CI ^l) |
| Omicron BA.4-5 - NT50 (titre) ^d | 294 | 180 (61.2) (55.4, 66.8) | 282 | 188 (66.7) (60.8, 72.1) | 273 | 127 (46.5) (40.5, 52.6) | -3.03 (-9.68, 3.63) ^m | 26.77 (19.59, 33.95) ⁿ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥ 4 × LLOQ is considered a seroresponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8.
- N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage.
- 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, ≥ median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is > -10%.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is > -5%.

Table 5. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

| SARS-CoV-2 neutralization assay | Sampling time point ^a | Comirnaty Original/Omicron BA.4-5 | | | | | |
|--|----------------------------------|-----------------------------------|---|----------------------------|---|---------------------------|---|
| | | 12 through 17 years of age | | 18 through 55 years of age | | 56 years of age and older | |
| | | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) | n ^b | GMT ^c (95% CI ^c) |
| Omicron BA.4-5 - NT50 (titre) ^d | Pre-vaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference strain - NT50 (titre) ^d | Pre-vaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19

mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|--|
| Subgroup | COVID-19 mRNA Vaccine N^a = 18 198 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a = 18 325 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI)^e |
| All participants | 8 2.214 (17 411) | 162 2.222 (17 511) | 95.0 (90.0, 97.9) |
| 16 to 64 years | 7 1.706 (13 549) | 143 1.710 (13 618) | 95.1 (89.6, 98.1) |
| 65 years and older | 1 0.508 (3 848) | 19 0.511 (3 880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3 074) | 14 0.406 (3 095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 7.

Table 7. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

| Subgroup | COVID-19 mRNA Vaccine N^a=20 998 Cases n1^b Surveillance time^c (n2^d) | Placebo N^a=21 096 Cases n1^b Surveillance time^c (n2^d) | Vaccine efficacy % (95% CI^e) |
|-------------------------------|---|---|--|
| All participants ^f | 77 6.247 (20 712) | 850 6.003 (20 713) | 91.3 (89.0, 93.2) |
| 16 to 64 years | 70 4.859 (15 519) | 710 4.654 (15 515) | 90.6 (87.9, 92.7) |
| 65 years and older | 7 1.233 (4 192) | 124 1.202 (4 226) | 94.5 (88.3, 97.8) |
| 65 to 74 years | 6 0.994 (3 350) | 98 0.966 (3 379) | 94.1 (86.6, 97.9) |
| 75 years and older | 1 0.239 (842) | 26 0.237 (847) | 96.2 (76.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 8) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 8. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

| | COVID-19 mRNA Vaccine Cases n1^a Surveillance time (n2^b) | Placebo Cases n1^a Surveillance time (n2^b) | Vaccine efficacy % (95% CI)^c |
|----------------------------------|--|--|--|
| After Dose 1 ^d | 1 8.439 ^e (22 505) | 30 8.288 ^e (22 435) | 96.7 (80.3, 99.9) |
| 7 days after Dose 2 ^f | 1 6.522 ^g (21 649) | 21 6.404 ^g (21 730) | 95.3 (70.9, 99.9) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.

f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.

g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without

evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Efficacy and immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 9. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 9. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

| First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|--|--|
| | COVID-19 mRNA Vaccine 10 mcg/dose N^a=1 305 Cases n¹^b Surveillance time^c (n²^d) | Placebo N^a=663 Cases n¹^b Surveillance time^c (n²^d) | Vaccine efficacy % (95% CI) |
| Children 5 to 11 years of age | 3 0.322 (1 273) | 16 0.159 (637) | 90.7 (67.7, 98.3) |

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2 703 participants who received the vaccine and 42 cases out of 1 348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3 018 who received vaccine and 42 cases in 1 511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age (i.e. 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 10.

Table 10. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

| | | COVID-19 mRNA Vaccine | | 5 to 11 years/ 16 to 25 years | |
|--|-------------------------|---|--|--|--|
| | | 10 mcg/dose 5 to 11 years N ^a =264 | 30 mcg/dose 16 to 25 years N ^a =253 | | |
| | Time point ^b | GMT ^c (95% CI ^c) | GMT ^c (95% CI ^c) | GMR ^d (95% CI ^d) | Met immunobridging objective ^e (Y/N) |
| Geometric mean 50% neutralizing titre^f (GMT^c) | 1 month after Dose 2 | 1 197.6 (1 106.1, 1 296.6) | 1 146.5 (1 045.5, 1 257.2) | 1.04 (0.93, 1.18) | Y |

| | Time point ^b | n ^g (%) (95% CI ^h) | n ^g (%) (95% CI ^h) | Difference % ⁱ (95% CI ^j) | Met immunobridging objective ^k (Y/N) |
|---|-------------------------|--|--|--|--|
| Seroresponse rate (%) for 50% neutralizing titre^f | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

Immunogenicity in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after booster dose

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 11.

Table 11. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

| Assay | Sampling time point ^a | | 1 month after booster dose/ 1 month after dose 2 GMR ^d (95% CI ^d) |
|--|---|---|---|
| | 1 month after booster dose (n ^b =67) GMT ^c (95% CI ^c) | 1 month after dose 2 (n ^b =96) GMT ^c (95% CI ^c) | |
| SARS-CoV-2 neutralization assay - NT50 (titre) | 2 720.9 (2 280.1, 3 247.0) | 1 253.9 (1 116.0, 1 408.9) | 2.17 (1.76, 2.68) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

Efficacy and immunogenicity of a 3-dose primary course in infants and children 6 months to 4 years of age

The efficacy analysis of Study 3 was performed across the combined population of participants 6 months through 4 years of age based on cases confirmed among 873 participants in the COVID-19 mRNA Vaccine group and 381 participants in the placebo group (2:1 randomization ratio) who received all 3 doses of study intervention during the blinded follow-up period when the Omicron variant of SARS-CoV-2 (BA.2) was the predominant variant in circulation (data cut-off date of 17 June 2022).

The vaccine efficacy results after Dose 3 in participants 6 months through 4 years of age are presented in Table 12.

Table 12. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Phase 2/3 – 6 Months to 4 Years of Age – Evaluable Efficacy (3-Dose) Population

| First COVID-19 occurrence from 7 days after Dose 3 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|--|--|---|--|
| Subgroup | COVID-19 mRNA Vaccine 3 mcg/Dose N ^a =873 Cases n ^{1b} Surveillance Time ^c (n ^{2d}) | Placebo N ^a =381 Cases n ^{1b} Surveillance Time ^c (n ^{2d}) | Vaccine Efficacy % (95% CI ^e) |
| 6 months through 4 years ^e | 13 0.124 (794) | 21 0.054 (351) | 73.2 (43.8, 87.6) |
| 2 through 4 years | 9 0.081 (498) | 13 0.033 (204) | 71.8 (28.6, 89.4) |
| 6 months through 23 months | 4 0.042 (296) | 8 0.020 (147) | 75.8 (9.7, 94.7) |

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (i.e. negative N-binding antibody [serum] result at Dose 1, 1 month post-Dose 2 (if available), Dose 3 (if available) visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 3) and had no medical history of COVID-19 were included in the analysis.
 - a. N = number of participants in the specified group.
 - b. n1 = Number of participants meeting the endpoint definition.
 - c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 3 to the end of the surveillance period.
 - d. n2 = Number of participants at risk for the endpoint.
 - e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Vaccine efficacy in participants with or without prior SARS-CoV-2 infection was similar to those participants without prior SARS-CoV-2 infection.

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 12 cases (8 COVID-19 mRNA Vaccine and 4 placebo) among participants 6 months to 4 years of age. Among participants 6 months through 23 months of age, severe COVID-19 criteria were fulfilled for 3 cases (2 COVID-19 mRNA Vaccine and 1 placebo).

Immunogenicity analyses have been performed in the immunobridging subset of 82 Study 3 participants 6 to 23 months of age and 143 Study 3 participants 2 to 4 years of age without evidence of infection up to 1 month after Dose 3 based on a data cut-off date of 29 April 2022.

SARS-CoV-2 50% neutralising antibody titres (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 6 to 23 months of age and 2 to 4 years of age from Study 3 at 1 month after the 3-dose primary course and a randomly selected subset from Study 2 Phase 2/3 participants 16 to 25 years of age at 1 month after the 2-dose primary course, using a microneutralisation assay against the reference strain (USA_WA1/2020).

The primary immunobridging analyses compared the geometric mean titres (using a geometric mean ratio [GMR]) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 to 23 months of age and 2 to 4 years of age and up to 1 month after Dose 2 in participants 16 to 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference for both age groups (Table 13).

Table 13. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset – participants 6 months to 4 years of age (Study 3) 1 month after Dose 3 and participants 16 to 25 years of age (Study 2) 1 month after Dose 2 – without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

| SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course | | | | | | | |
|---|----------------|---|-----------------------------|----------------|---|--|--|
| SARS-CoV-2 neutralization assay - NT50 (titre) ^e | | | | | | | |
| Age | N ^a | GMT ^b (95% CI ^b) (1 month after Dose 3) | Age | N ^a | GMT ^b (95% CI ^b) (1 month after Dose 2) | Age | GMR ^{c,d} (95% CI) |
| 2 to 4 years | 143 | 1 535.2 (1 388.2, 1 697.8) | 16 to 25 years of age | 170 | 1 180.0 (1 066.6, 1 305.4) | 2 to 4 years/16 to 25 years of age | 1.30 (1.13, 1.50) |
| 6 to 23 months | 82 | 1 406.5 (1 211.3, 1 633.1) | 16 to 25 years of age | 170 | 1 180.0 (1 066.6, 1 305.4) | 6 to 23 months years/16 to 25 years of age | 1.19 (1.00, 1.42) |
| Difference in percentages of participants with seroresponse at 1 month after vaccination course | | | | | | | |
| SARS-CoV-2 neutralization assay - NT50 (titre) ^e | | | | | | | |
| Age | N ^a | n ^f (%) (95% CI ^g) (1 month after Dose 3) | Age | N ^a | n ^f (%) (95% CI ^g) (1 month after Dose 2) | Age | Difference in seroresponse rates % ^h (95% CI) ^j |
| 2 to 4 years | 141 | 141(100.0) (97.4, 100.0) | 16 to 25 years of age | 170 | 168 (98.8) (95.8, 99.9) | 2 to 4 years/16 to 25 years of age | 1.2 (1.5, 4.2) |
| 6 to 23 months | 80 | 80 (100.0) (95.5, 100.0) | 16 to 25 years of age | 170 | 168 (98.8) (95.8, 99.9) | 6 to 23 months years/16 to 25 years of age | 1.2 (3.4, 4.2) |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [(i.e. N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point for GMTs and number of participants with valid and determinate assay results for the specified assay at both baseline and the given dose/sampling time point for seroresponse rates.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (younger age group minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).

- d. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on GMR is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- f. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
- g. Exact 2-sided CI based on the Clopper and Pearson method.
- h. Difference in proportions, expressed as a percentage (younger age group minus 16 to 25 years of age).
- i. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- j. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The vaccine will be received frozen at -90 °C to -60 °C.

Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

18 months when stored at -90 °C to -60 °C.

Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials

10 weeks storage and transportation at 2 °C to 8 °C within the 18-month shelf life.

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, and within the 10 weeks storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

0.48 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a yellow flip-off plastic cap with aluminium seal. Each vial contains 3 doses, see section 6.6.

Pack size: 10 vials

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty KP.2 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **yellow plastic cap** and the product **name is Comirnaty KP.2 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label, or a different cap colour, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.

- The thawed vaccine must be diluted in its original vial with **1.1 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.1 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.3 mL doses

- After dilution, the vial contains 1.58 mL from which **3 doses** of **0.3 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw **0.3 mL** of Comirnaty KP.2 for infants and children aged 6 months to 4 years. **Standard syringes and/or needles** can be used in order to extract 3 doses from a single vial.
- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
 An der Goldgrube 12
 55131 Mainz
 Germany
 Phone: +49 6131 9084-0
 Fax: +49 6131 9084-2121
 service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/042

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
 Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance(s)

BioNTech Manufacturing Marburg GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

Pfizer Ireland Pharmaceuticals
Grange Castle Business Park
Clondalkin
Dublin 22
Ireland

Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC
1 Burt Road
Andover, MA 01810
USA

Name and address of the manufacturers responsible for batch release

BioNTech Manufacturing GmbH
Kupferbergterrasse 17 - 19
55116 Mainz
Germany

Pfizer Manufacturing Belgium NV
Rijksweg 12
Puurs-Sint-Amands, 2870
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)

BOX LABEL (195 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY 30 micrograms/dose dispersion for injection
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
tozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/013

Multidose vials

EU/1/20/1528/002 10 multidose vials

EU/1/20/1528/003 195 multidose vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC

SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY 30 mcg injection
COVID-19 mRNA Vaccine
tozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials
1 dose

Multidose vials
6 doses 30 mcg

6. OTHER

Multidose vials
Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)
BOX LABEL (195 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY 10 micrograms/dose concentrate for dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
tozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials
195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/004 10 multidose vials
EU/1/20/1528/005 195 multidose vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY 10 mcg sterile concentrate
COVID-19 mRNA Vaccine
tozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 10 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY 3 micrograms/dose concentrate for dispersion for injection
children 6 months to 4 years
COVID-19 mRNA Vaccine
tozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)

Expiry date at 2 °C to 8 °C:

(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.

Store in the original package in order to protect from light.

After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

BioNTech Manufacturing GmbH

An der Goldgrube 12

55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY 3 mcg sterile concentrate
COVID-19 mRNA Vaccine
tozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 3 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)

BOX LABEL (195 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
tozinameran/famtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 15 micrograms tozinameran and 15 micrograms famtozinameran.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



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6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/014

Multidose vials

EU/1/20/1528/008 10 multidose vials

EU/1/20/1528/009 195 multidose vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC

SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Original/Omicron BA.4-5 15/15 mcg injection
COVID-19 mRNA Vaccine
tozinameran/famtozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials
1 dose

Multidose vials
6 doses 15/15 mcg

6. OTHER

Multidose vials
Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)
BOX LABEL (195 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
tozinameran/famtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.
One dose contains 5 micrograms tozinameran and 5 micrograms famtozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials
195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/011 10 multidose vials
EU/1/20/1528/012 195 multidose vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Original/Omicron BA.4-5 5/5 mcg sterile concentrate
COVID-19 mRNA Vaccine
tozinameran/famtozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 5/5 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
tozinameran/famtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 5 micrograms tozinameran and 5 micrograms famtozinameran.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan code for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials
EU/1/20/1528/015

Multidose vials
EU/1/20/1528/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Original/Omicron BA.4-5 5/5 mcg injection
COVID-19 mRNA Vaccine
tozinameran/famtozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials
1 dose

Multidose vials
6 doses 5/5 mcg

6. OTHER

Multidose vials
Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection
children 6 months to 4 years
COVID-19 mRNA Vaccine
tozinameran/famtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.
One dose contains 1.5 micrograms tozinameran and 1.5 micrograms famtozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/017

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Original/Omicron BA.4-5 1.5/1.5 mcg sterile concentrate
COVID-19 mRNA Vaccine
tozinameran/famtozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 1.5/1.5 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)

BOX LABEL (195 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Omicron XBB.1.5 30 micrograms/dose dispersion for injection
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
raxtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 30 micrograms raxtozinameran.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/018

Multidose vials

EU/1/20/1528/019 10 multidose vials

EU/1/20/1528/020 195 multidose vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC

SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Omicron XBB.1.5 30 mcg injection
COVID-19 mRNA Vaccine
raxtozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials
1 dose

Multidose vials
6 doses 30 mcg

6. OTHER

Multidose vials
Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (plastic pre-filled syringe)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Omicron XBB.1.5 30 micrograms/dose dispersion for injection in pre-filled syringe
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
raxtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 1 dose of 0.3 mL. One dose contains 30 micrograms raxtozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection
10 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use.
Single use



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/025

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (plastic pre-filled syringe)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Omicron XBB.1.5 30 mcg injection
COVID-19 mRNA Vaccine
raxtozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP (at -90 °C to -60 °C)

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (glass pre-filled syringe)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Omicron XBB.1.5 30 micrograms/dose dispersion for injection in pre-filled syringe
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
raxtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 1 dose of 0.3 mL. One dose contains 30 micrograms raxtozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

10 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.

Read the package leaflet before use.
Single use



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at 2 °C to 8 °C)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/027

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (glass pre-filled syringe)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Omicron XBB.1.5 30 mcg injection
COVID-19 mRNA Vaccine
raxtozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP (at 2 °C to 8 °C)

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
raxtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.
One dose contains 10 micrograms raxtozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride,
sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/021

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Omicron XBB.1.5 10 mcg sterile concentrate
COVID-19 mRNA Vaccine
raxtozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 10 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Omicron XBB.1.5 10 micrograms/dose dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
raxtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 10 micrograms raxtozinameran.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials
EU/1/20/1528/022

Multidose vials
EU/1/20/1528/023

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Omicron XBB.1.5 10 mcg injection
COVID-19 mRNA Vaccine
raxtozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials
1 dose

Multidose vials
6 doses 10 mcg

6. OTHER

Multidose vials
Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection
children 6 months to 4 years
COVID-19 mRNA Vaccine
raxtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains **10** doses of **0.2 mL**.
One dose contains 3 micrograms raxtozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with **2.2 mL** sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/024

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Omicron XBB.1.5 3 mcg sterile concentrate
COVID-19 mRNA Vaccine
raxtozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses of 0.2 mL after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection
children 6 months to 4 years
COVID-19 mRNA Vaccine
raxtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains **3** doses of **0.3 mL**.
One dose contains 3 micrograms raxtozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with **1.1 mL** sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/026

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Omicron XBB.1.5 3 mcg sterile concentrate
COVID-19 mRNA Vaccine
raxtozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 doses of 0.3 mL after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY JN.1 30 micrograms/dose dispersion for injection
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
bretovameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 30 micrograms bretovameran.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials
EU/1/20/1528/028

Multidose vials
EU/1/20/1528/029

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY JN.1 30 mcg injection
COVID-19 mRNA Vaccine
bretovameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials
1 dose

Multidose vials
6 doses 30 mcg

6. OTHER

Multidose vials
Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (plastic pre-filled syringe)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY JN.1 30 micrograms/dose dispersion for injection in pre-filled syringe
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
bretovameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 1 dose of 0.3 mL. One dose contains 30 micrograms bretovameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection
10 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use.
Single use



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/031

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (plastic pre-filled syringe)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY JN.1 30 mcg injection
COVID-19 mRNA Vaccine
bretovameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP (at -90 °C to -60 °C)

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (glass pre-filled syringe)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY JN.1 30 micrograms/dose dispersion for injection in pre-filled syringe
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
bretovameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 1 dose of 0.3 mL. One dose contains 30 micrograms bretovameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

10 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Read the package leaflet before use.
Single use



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at 2 °C to 8 °C)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/030

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (glass pre-filled syringe)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY JN.1 30 mcg injection
COVID-19 mRNA Vaccine
bretovameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP (at 2 °C to 8 °C)

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY JN.1 10 micrograms/dose concentrate for dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
bretovameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.
One dose contains 10 micrograms bretovameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/034

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY JN.1 10 mcg sterile concentrate
COVID-19 mRNA Vaccine
bretovameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 10 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY JN.1 10 micrograms/dose dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
bretovameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 10 micrograms bretovameran.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials
EU/1/20/1528/032

Multidose vials
EU/1/20/1528/033

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY JN.1 10 mcg injection
COVID-19 mRNA Vaccine
bretovameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials
1 dose

Multidose vials
6 doses 10 mcg

6. OTHER

Multidose vials
Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY JN.1 3 micrograms/dose concentrate for dispersion for injection
children 6 months to 4 years
COVID-19 mRNA Vaccine
bretovameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains **10** doses of **0.2 mL**.
One dose contains 3 micrograms bretovameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with **2.2 mL** sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/036

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY JN.1 3 mcg sterile concentrate
COVID-19 mRNA Vaccine
bretovameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses of 0.2 mL after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY JN.1 3 micrograms/dose concentrate for dispersion for injection
children 6 months to 4 years
COVID-19 mRNA Vaccine
bretovameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains **3** doses of **0.3 mL**.
One dose contains 3 micrograms bretovameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with **1.1 mL** sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/035

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY JN.1 3 mcg sterile concentrate
COVID-19 mRNA Vaccine
bretovameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 doses of 0.3 mL after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY KP.2 30 micrograms/dose dispersion for injection
adults and adolescents from 12 years
COVID-19 mRNA Vaccine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 30 micrograms mRNA encoding KP.2.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials
EU/1/20/1528/037

Multidose vials
EU/1/20/1528/038

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY KP.2 30 mcg injection
COVID-19 mRNA Vaccine
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials

1 dose

Multidose vials

6 doses 30 mcg

6. OTHER

Multidose vials

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (glass pre-filled syringe)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY KP.2 30 micrograms/dose dispersion for injection in pre-filled syringe
adults and adolescents from 12 years
COVID-19 mRNA Vaccine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 1 dose of 0.3 mL. One dose contains 30 micrograms mRNA encoding KP.2.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

10 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Read the package leaflet before use.
Single use



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at 2 °C to 8 °C)

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/039

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (glass pre-filled syringe)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY KP.2 30 mcg injection
COVID-19 mRNA Vaccine
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP (at 2 °C to 8 °C)

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY KP.2 10 micrograms/dose dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 10 micrograms mRNA encoding KP.2.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/040

Multidose vials

EU/1/20/1528/041

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY KP.2 10 mcg injection
COVID-19 mRNA Vaccine
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials

1 dose

Multidose vials

6 doses 10 mcg

6. OTHER

Multidose vials

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY KP.2 3 micrograms/dose concentrate for dispersion for injection
children 6 months to 4 years
COVID-19 mRNA Vaccine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains **3** doses of **0.3 mL**.
One dose contains 3 micrograms mRNA encoding KP.2.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with **1.1 mL** sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)

Expiry date at 2 °C to 8 °C:

(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.

Store in the original package in order to protect from light.

After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

BioNTech Manufacturing GmbH

An der Goldgrube 12

55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/042

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY KP.2 3 mcg sterile concentrate
COVID-19 mRNA Vaccine
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 doses of 0.3 mL after dilution

6. OTHER

Discard time:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Comirnaty 30 micrograms/dose dispersion for injection Adults and adolescents from 12 years COVID-19 mRNA Vaccine tozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for
2. What you need to know before you receive Comirnaty
3. How Comirnaty is given
4. Possible side effects
5. How to store Comirnaty
6. Contents of the pack and other information

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty 30 micrograms/dose dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty

Comirnaty should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.

- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty 30 micrograms/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Comirnaty may be given at the same time as a flu vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

Comirnaty can be used during pregnancy. A large amount of information from pregnant women vaccinated with Comirnaty during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen.

Comirnaty can be given during breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty is given

Comirnaty is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty.

If you have any further questions on the use of Comirnaty, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)

- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Single dose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called tozinameran.
 - A single dose vial contains 1 dose of 0.3 mL with 30 micrograms tozinameran each.
 - A multidose vial contains 6 doses of 0.3 mL with 30 micrograms tozinameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal.

Single dose vials pack size: 10 vials

Multidose vials pack sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

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- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:

<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty 30 micrograms/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C. Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty 10 micrograms/dose concentrate for dispersion for injection Children 5 to 11 years COVID-19 mRNA Vaccine tozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for
2. What you need to know before your child receives Comirnaty
3. How Comirnaty is given
4. Possible side effects
5. How to store Comirnaty
6. Contents of the pack and other information

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty 10 micrograms/dose concentrate for dispersion for injection is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty

Comirnaty should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.
- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.

- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty 10 micrograms/dose concentrate for dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

Comirnaty can be used during pregnancy. A large amount of information from pregnant women vaccinated with Comirnaty during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen.

Comirnaty can be given during breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty is given

Comirnaty is given after dilution as an injection of 0.2 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty until at least 3 months after the most recent dose.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty.

If you have any further questions on the use of Comirnaty, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)

- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called tozinameran. After dilution, the vial contains 10 doses of 0.2 mL with 10 micrograms tozinameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and an orange flip-off plastic cap with aluminium seal.

Pack sizes: 10 vials or 195 vials
Not all pack sizes may be marketed.

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- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
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- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

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Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty intramuscularly after dilution as a single dose of 0.2 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- Verify that the vial has an **orange plastic cap** and the product name is **Comirnaty 10 micrograms/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty for children aged 5 to 11 years.
Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty 3 micrograms/dose concentrate for dispersion for injection Infants and children 6 months to 4 years COVID-19 mRNA Vaccine tozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for
2. What you need to know before your child receives Comirnaty
3. How Comirnaty is given
4. Possible side effects
5. How to store Comirnaty
6. Contents of the pack and other information

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty 3 micrograms/dose concentrate for dispersion for injection is given to infants and children from 6 months to 4 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty

Comirnaty should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.
- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.

- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty 3 micrograms/dose concentrate for dispersion for injection is not recommended for children aged 5 years to 11 years.

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

Comirnaty 3 micrograms/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Package Leaflet for those formulations.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty is given

If your infant is from 6 months to less than 12 months of age, he/she will be given Comirnaty after dilution as an injection of 0.2 mL into a muscle of the thigh. If your infant or child is 1 year of age or older, he/she will be given Comirnaty after dilution as an injection of 0.2 mL into a muscle of the thigh or into a muscle of the upper arm.

If your child has not completed a COVID-19 primary vaccination course or has not been infected by COVID-19 in the past, your child will receive a maximum of 3 injections (the total number of doses required as primary course). It is recommended to receive the second dose 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If your child has previously completed a COVID-19 primary vaccination course or has had COVID-19, your child will receive 1 injection. If your child was previously vaccinated with a COVID-19 vaccine, your child should not receive a dose of Comirnaty until at least 3 months after the most recent dose.

If your child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty.

Interchangeability

Your child may receive any previous or current Comirnaty vaccine for the primary course. Your child should not receive more than the total number of doses needed as primary course. Your child should only be administered the primary course once.

If you have any further questions on the use of Comirnaty, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- irritability (6 months to < 2 years)
- injection site: pain/tenderness, swelling
- tiredness, headache
- drowsiness (6 months to < 2 years)
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 6 months to 11 years)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash ('common' for 6 months to < 2 years) or itching
- decreased appetite ('very common' for 6 months to < 2 years)
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called tozinameran. After dilution, the vial contains 10 doses of 0.2 mL with 3 micrograms tozinameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a maroon flip-off plastic cap with aluminium seal.

Pack size: 10 vials

Marketing Authorisation Holder

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service@biontech.de

Manufacturers

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Pfizer Manufacturing Belgium NV
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Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Tél/Tel: +32 (0)2 554 62 11
- **България:** Пфайзер Люксембург САРЛ, Клон, България, Тел: +359 2 970 4333
- **Česká republika:** Pfizer, spol. s r.o., Tel: +420 283 004 111
- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
- **Deutschland:** BioNTech Manufacturing GmbH, Tel: +49 6131 90840
- **Eesti:** Pfizer Luxembourg SARL Eesti filiaal, Tel: +372 666 7500

- **Ελλάδα:** Pfizer Ελλάς Α.Ε., Τηλ.: +30 210 6785 800
- **España:** Pfizer, S.L., Tel: +34914909900
- **France:** Pfizer, Tél +33 1 58 07 34 40
- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
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- **Ísland:** Icepharma hf, Simi: +354 540 8000
- **Italia:** Pfizer S.r.l., Tel: +39 06 33 18 21
- **Κύπρος:** Pfizer Ελλάς Α.Ε. (Cyprus Branch), Τηλ: +357 22 817690
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- **Lietuva:** Pfizer Luxembourg SARL filialas Lietuvoje, Tel. +370 52 51 4000
- **Magyarország:** Pfizer Kft, Tel: +36 1 488 3700
- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

If the child has not completed a COVID-19 primary vaccination course or does not have a history of prior SARS-CoV-2 infection, administer Comirnaty intramuscularly after dilution as a primary course of maximum 3 doses (the total number of doses required as primary course) (0.2 mL each); the second dose administered 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If the child has completed a COVID-19 primary vaccination course or has a history of prior SARS-CoV-2 infection, administer Comirnaty intramuscularly after dilution a single dose of 0.2 mL. If the individual was previously vaccinated with a COVID-19 vaccine, the individual should receive a dose of Comirnaty at least 3 months after the most recent dose.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty for infants and children aged 6 months to 4 years. **Low dead-volume syringes and/or needles** should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection Adults and adolescents from 12 years COVID-19 mRNA Vaccine tozinameran/famtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for
2. What you need to know before you receive Comirnaty Original/Omicron BA.4-5
3. How Comirnaty Original/Omicron BA.4-5 is given
4. Possible side effects
5. How to store Comirnaty Original/Omicron BA.4-5
6. Contents of the pack and other information

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for

Comirnaty Original/Omicron BA.4-5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2. It is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Original/Omicron BA.4-5 does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty Original/Omicron BA.4-5

Comirnaty Original/Omicron BA.4-5 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.

- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Original/Omicron BA.4-5 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty Original/Omicron BA.4-5. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Original/Omicron BA.4-5

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Comirnaty Original/Omicron BA.4-5 may be given at the same time as a flu vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Original/Omicron BA.4-5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty Original/Omicron BA.4-5 is given

Comirnaty Original/Omicron BA.4-5 is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty Original/Omicron BA.4-5 until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty Original/Omicron BA.4-5.

If you have any further questions on the use of Comirnaty Original/Omicron BA.4-5, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Original/Omicron BA.4-5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Original/Omicron BA.4-5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Single dose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Original/Omicron BA.4-5 contains

- The active substances of COVID-19 mRNA Vaccine (nucleoside modified) are called tozinameran and famtozinameran.
 - A single dose vial contains 1 dose of 0.3 mL with 15 micrograms of tozinameran (Original) and 15 micrograms of famtozinameran (Omicron BA.4-5) per dose.
 - A multidose vial contains 6 doses of 0.3 mL with 15 micrograms of tozinameran (Original) and 15 micrograms of famtozinameran (Omicron BA.4-5) per dose.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty Original/Omicron BA.4-5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal.

Single dose vials pack size: 10 vials

Multidose vials pack sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
- **Deutschland:** BioNTech Manufacturing GmbH, Tel: +49 6131 90840
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- **Ελλάδα:** Pfizer Ελλάς Α.Ε., Τηλ.: +30 210 6785 800
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- **Ísland:** Icepharma hf, Simi: +354 540 8000
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- **Κύπρος:** Pfizer Ελλάς Α.Ε. (Cyprus Branch), Τηλ: +357 22 817690
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- **Lietuva:** Pfizer Luxembourg SARL filialas Lietuvoje, Tel. +370 52 51 4000
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- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
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- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
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- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty Original/Omicron BA.4-5 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty Original/Omicron BA.4-5.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.

- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection

Children 5 to 11 years
COVID-19 mRNA Vaccine
tozinameran/famtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for
2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5
3. How Comirnaty Original/Omicron BA.4-5 is given
4. Possible side effects
5. How to store Comirnaty Original/Omicron BA.4-5
6. Contents of the pack and other information

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for

Comirnaty Original/Omicron BA.4-5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2. It is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Original/Omicron BA.4-5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5

Comirnaty Original/Omicron BA.4-5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.
- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.

- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Original/Omicron BA.4-5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty Original/Omicron BA.4-5. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Original/Omicron BA.4-5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Original/Omicron BA.4-5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Original/Omicron BA.4-5 is given

Comirnaty Original/Omicron BA.4-5 is given after dilution as an injection of 0.2 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty Original/Omicron BA.4-5 until at least 3 months after the most recent dose.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty Original/Omicron BA.4-5.

If you have any further questions on the use of Comirnaty Original/Omicron BA.4-5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Original/Omicron BA.4-5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoaesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Original/Omicron BA.4-5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Original/Omicron BA.4-5 contains

- The active substances of COVID-19 mRNA Vaccine (nucleoside modified) are called tozinameran and famtozinameran. After dilution, the vial contains 10 doses of 0.2 mL with 5 micrograms of tozinameran (Original) and 5 micrograms of famtozinameran (Omicron BA.4-5) per dose.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty Original/Omicron BA.4-5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and an orange flip-off plastic cap with aluminium seal.

Pack sizes: 10 vials or 195 vials
Not all pack sizes may be marketed.

Marketing Authorisation Holder

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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- **Česká republika:** Pfizer, spol. s r.o., Tel: +420 283 004 111
- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
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- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
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- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
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- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Administer Comirnaty Original/Omicron BA.4-5 intramuscularly after dilution as a single dose of 0.2 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has an **orange plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty Original/Omicron BA.4-5 for children aged 5 to 11 years. **Low dead-volume syringes and/or needles** should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection Children 5 to 11 years COVID-19 mRNA Vaccine tozinameran/famtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for
2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5
3. How Comirnaty Original/Omicron BA.4-5 is given
4. Possible side effects
5. How to store Comirnaty Original/Omicron BA.4-5
6. Contents of the pack and other information

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for

Comirnaty Original/Omicron BA.4-5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2. It is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Original/Omicron BA.4-5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5

Comirnaty Original/Omicron BA.4-5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.
- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.

- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Original/Omicron BA.4-5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty Original/Omicron BA.4-5. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Original/Omicron BA.4-5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Original/Omicron BA.4-5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Original/Omicron BA.4-5 is given

Comirnaty Original/Omicron BA.4-5 is given as an injection of 0.3 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty Original/Omicron BA.4-5 until at least 3 months after the most recent dose.

If your child is immunocompromised, your child may receive additional doses of Comirnaty Original/Omicron BA.4-5.

If you have any further questions on the use of Comirnaty Original/Omicron BA.4-5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Original/Omicron BA.4-5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Original/Omicron BA.4-5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Single dose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Original/Omicron BA.4-5 contains

- The active substances of COVID-19 mRNA Vaccine (nucleoside modified) are called tozinameran and famtozinameran.
 - A single dose vial contains 1 dose of 0.3 mL with 5 micrograms of tozinameran (Original) and 5 micrograms of famtozinameran (Omicron BA.4-5) per dose.
 - A multidose vial contains 6 doses of 0.3 mL with 5 micrograms of tozinameran (Original) and 5 micrograms of famtozinameran (Omicron BA.4-5) per dose.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty Original/Omicron BA.4-5 looks like and contents of the pack

The vaccine is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal.

Single dose vials pack size: 10 vials

Multidose vials pack size: 10 vials

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
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This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Administer Comirnaty Original/Omicron BA.4-5 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **blue plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty Original/Omicron BA.4-5 for children aged 5 to 11 years.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection

Infants and children 6 months to 4 years

COVID-19 mRNA Vaccine

tozinameran/famtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for
2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5
3. How Comirnaty Original/Omicron BA.4-5 is given
4. Possible side effects
5. How to store Comirnaty Original/Omicron BA.4-5
6. Contents of the pack and other information

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for

Comirnaty Original/Omicron BA.4-5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2. It is given to infants and children from 6 months to 4 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Original/Omicron BA.4-5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5

Comirnaty Original/Omicron BA.4-5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.
- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.

- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Original/Omicron BA.4-5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty Original/Omicron BA.4-5, may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty Original/Omicron BA.4-5. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection is not recommended for children aged 5 years to 11 years.

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Original/Omicron BA.4-5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Package Leaflet for those formulations.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Original/Omicron BA.4-5 is given

If your infant is from 6 months to less than 12 months of age, he/she will be given Comirnaty Original/Omicron BA.4-5 after dilution as an injection of 0.2 mL into a muscle of the thigh. If your infant or child is 1 year of age or older, he/she will be given Comirnaty Original/Omicron BA.4-5 after dilution as an injection of 0.2 mL into a muscle of the thigh or into a muscle of the upper arm.

If your child has not completed a COVID-19 primary vaccination course or has not been infected by COVID-19 in the past, your child will receive a maximum of 3 injections (the total number of doses required as primary course). It is recommended to receive the second dose 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If your child has previously completed a COVID-19 primary vaccination course or has had COVID-19 your child will receive 1 injection. If your child was previously vaccinated with a COVID-19 vaccine, your child should not receive a dose of Comirnaty Original/Omicron BA.4-5 until at least 3 months after the most recent dose.

If your child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty Original/Omicron BA.4-5.

Interchangeability

Your child may receive any previous or current Comirnaty vaccine for the primary course. Your child should not receive more than the total number of doses needed as primary course. Your child should only be administered the primary course once.

If you have any further questions on the use of Comirnaty Original/Omicron BA.4-5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Original/Omicron BA.4-5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- irritability (6 months to < 2 years)
- injection site: pain/tenderness, swelling
- tiredness, headache
- drowsiness (6 months to < 2 years)
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 6 months to 11 years)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash ('common' for 6 months to < 2 years) or itching
- decreased appetite ('very common' for 6 months to < 2 years)
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Original/Omicron BA.4-5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Original/Omicron BA.4-5 contains

- The active substances of COVID-19 mRNA Vaccine (nucleoside modified) are called tozinameran and famtozinameran. After dilution, the vial contains 10 doses of 0.2 mL with 1.5 micrograms of tozinameran (Original) and 1.5 micrograms of famtozinameran (Omicron BA.4-5) per dose.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty Original/Omicron BA.4-5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a maroon flip-off plastic cap with aluminium seal.

Pack size: 10 vials

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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- **България:** Пфайзер Люксембург САРЛ, Клон, България, Тел: +359 2 970 4333
- **Česká republika:** Pfizer, spol. s r.o., Tel: +420 283 004 111
- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
- **Deutschland:** BioNTech Manufacturing GmbH, Tel: +49 6131 90840
- **Eesti:** Pfizer Luxembourg SARL Eesti filiaal, Tel: +372 666 7500
- **Ελλάδα:** Pfizer Ελλάς Α.Ε., Τηλ.: +30 210 6785 800
- **España:** Pfizer, S.L., Tel: +34914909900
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- **Ireland:** Pfizer Healthcare Ireland, Tel: 1800 633 363 (toll free), +44 (0)1304 616161
- **Ísland:** Icepharma hf, Simi: +354 540 8000
- **Italia:** Pfizer S.r.l., Tel: +39 06 33 18 21
- **Κύπρος:** Pfizer Ελλάς Α.Ε. (Cyprus Branch), Τηλ: +357 22 817690
- **Latvija:** Pfizer Luxembourg SARL filiāle Latvijā, Tel.: +371 670 35 775
- **Lietuva:** Pfizer Luxembourg SARL filialas Lietuvoje, Tel. +370 52 51 4000
- **Magyarország:** Pfizer Kft, Tel: +36 1 488 3700
- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

If the child has not completed a COVID-19 primary vaccination course or does not have a history of prior SARS-CoV-2 infection, administer Comirnaty Original/Omicron BA.4-5 intramuscularly after dilution as a primary course of maximum 3 doses (the total number of doses required as primary

course) (0.2 mL each); the second dose administered 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If the child has completed a COVID-19 primary vaccination course or has a history of prior SARS-CoV-2 infection, administer Comirnaty Original/Omicron BA.4-5 intramuscularly after dilution a single dose of 0.2 mL. If the individual was previously vaccinated with a COVID-19 vaccine, the individual should receive a dose of Comirnaty Original/Omicron BA.4-5 at least 3 months after the most recent dose.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty Original/Omicron BA.4-5 for infants and children aged 6 months to 4 years.

Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection Adults and adolescents from 12 years COVID-19 mRNA Vaccine raxtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Omicron XBB.1.5 is and what it is used for
2. What you need to know before you receive Comirnaty Omicron XBB.1.5
3. How Comirnaty Omicron XBB.1.5 is given
4. Possible side effects
5. How to store Comirnaty Omicron XBB.1.5
6. Contents of the pack and other information

1. What Comirnaty Omicron XBB.1.5 is and what it is used for

Comirnaty Omicron XBB.1.5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Omicron XBB.1.5 does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty Omicron XBB.1.5

Comirnaty Omicron XBB.1.5 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.

- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Omicron XBB.1.5 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty Omicron XBB.1.5 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty Omicron XBB.1.5. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Omicron XBB.1.5

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Comirnaty Omicron XBB.1.5 may be given at the same time as a flu vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Omicron XBB.1.5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty Omicron XBB.1.5 is given

Comirnaty Omicron XBB.1.5 is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty Omicron XBB.1.5 until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty Omicron XBB.1.5.

If you have any further questions on the use of Comirnaty Omicron XBB.1.5, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Omicron XBB.1.5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Omicron XBB.1.5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Single dose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Omicron XBB.1.5 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called raxtozinameran.
 - A single dose vial contains 1 dose of 0.3 mL with 30 micrograms raxtozinameran each.
 - A multidose vial contains 6 doses of 0.3 mL with 30 micrograms raxtozinameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty Omicron XBB.1.5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal.

Single dose vials pack size: 10 vials

Multidose vials pack sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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- **France:** Pfizer, Tél +33 1 58 07 34 40
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- **Ísland:** Icepharma hf, Simi: +354 540 8000
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- **Lietuva:** Pfizer Luxembourg SARL filialas Lietuvoje, Tel. +370 52 51 4000
- **Magyarország:** Pfizer Kft, Tel: +36 1 488 3700
- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
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- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Administer Comirnaty Omicron XBB.1.5 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty Omicron XBB.1.5.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection in pre-filled syringe (plastic)
Adults and adolescents from 12 years
COVID-19 mRNA Vaccine
raxtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Omicron XBB.1.5 is and what it is used for
2. What you need to know before you receive Comirnaty Omicron XBB.1.5
3. How Comirnaty Omicron XBB.1.5 is given
4. Possible side effects
5. How to store Comirnaty Omicron XBB.1.5
6. Contents of the pack and other information

1. What Comirnaty Omicron XBB.1.5 is and what it is used for

Comirnaty Omicron XBB.1.5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Omicron XBB.1.5 does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty Omicron XBB.1.5

Comirnaty Omicron XBB.1.5 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.

- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Omicron XBB.1.5 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty Omicron XBB.1.5 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty Omicron XBB.1.5. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Omicron XBB.1.5

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Comirnaty Omicron XBB.1.5 may be given at the same time as a flu vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Omicron XBB.1.5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk

for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty Omicron XBB.1.5 is given

Comirnaty Omicron XBB.1.5 is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty Omicron XBB.1.5 until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty Omicron XBB.1.5.

If you have any further questions on the use of Comirnaty Omicron XBB.1.5, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Omicron XBB.1.5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Omicron XBB.1.5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Frozen plastic pre-filled syringes: Must be thawed prior to use. A 10 pre-filled syringe pack can be thawed at 2 °C to 8 °C. It may take 2 hours to thaw. Ensure pre-filled syringes are completely thawed prior to use.

Alternatively, a 10 pre-filled syringe pack may be thawed for 60 minutes at room temperature (up to 30 °C).

If an individual pre-filled syringe is thawed outside the carton at room temperature (up to 30 °C), the pre-filled syringe must be used immediately.

Thawed (previously frozen) plastic pre-filled syringes: Once removed from the freezer, the pre-filled syringes can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). Upon moving the pre-filled syringes to 2 °C to 8 °C storage, update the expiry date on the carton. If received at 2 °C to 8 °C, check that the expiry date has been updated. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the thawed pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Omicron XBB.1.5 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called raxtozinameran.
 - Each pre-filled syringe contains 1 dose of 0.3 mL with 30 micrograms raxtozinameran.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty Omicron XBB.1.5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a pre-filled syringe (1 mL long cyclic-olefin copolymer plastic syringe) with plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber) without needle.

Pack size: 10 pre-filled syringes

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- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
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- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty Omicron XBB.1.5 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

Instructions applicable to pre-filled syringes

Plastic pre-filled syringe

- Frozen pre-filled syringes must be completely thawed prior to use.
 - A 10 pre-filled syringe pack can be thawed at 2 °C to 8 °C. It may take 2 hours to thaw.
 - Alternatively, a carton of 10 frozen pre-filled syringes may be thawed for 60 minutes at room temperature (up to 30 °C).
- If an individual pre-filled syringe is thawed outside the carton at room temperature (up to 30 °C), this must be used immediately.
- Upon moving the pre-filled syringes to 2 °C to 8 °C storage, update the expiry date on the carton. If received at 2 °C to 8 °C, check that the expiry date has been updated.
- Thawed (previously frozen) pre-filled syringes can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). Once thawed, the vaccine cannot be re-frozen.
- Prior to use, the thawed pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.
- Remove tip cap by slowly turning the cap counterclockwise. Do not shake. Attach a needle appropriate for intramuscular injection and administer the entire volume.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection in pre-filled syringe (glass)

Adults and adolescents from 12 years

COVID-19 mRNA Vaccine

raxtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Omicron XBB.1.5 is and what it is used for
2. What you need to know before you receive Comirnaty Omicron XBB.1.5
3. How Comirnaty Omicron XBB.1.5 is given
4. Possible side effects
5. How to store Comirnaty Omicron XBB.1.5
6. Contents of the pack and other information

1. What Comirnaty Omicron XBB.1.5 is and what it is used for

Comirnaty Omicron XBB.1.5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Omicron XBB.1.5 does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty Omicron XBB.1.5

Comirnaty Omicron XBB.1.5 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.

- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Omicron XBB.1.5 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty Omicron XBB.1.5 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty Omicron XBB.1.5. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Omicron XBB.1.5

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Comirnaty Omicron XBB.1.5 may be given at the same time as a flu vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Omicron XBB.1.5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty Omicron XBB.1.5 is given

Comirnaty Omicron XBB.1.5 is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty Omicron XBB.1.5 until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty Omicron XBB.1.5.

If you have any further questions on the use of Comirnaty Omicron XBB.1.5, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Omicron XBB.1.5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Omicron XBB.1.5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP.

Store at 2 °C to 8 °C. DO NOT FREEZE.

Store in the original package in order to protect from light.

The vaccine will be received and stored at 2 °C to 8 °C (refrigerated only).

Prior to use, pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Omicron XBB.1.5 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called raxtozinameran.
 - Each pre-filled syringe contains 1 dose of 0.3 mL with 30 micrograms raxtozinameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty Omicron XBB.1.5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a pre-filled syringe (type I glass syringe) with plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber) without needle.

Pack size: 10 pre-filled syringes

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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty Omicron XBB.1.5 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

Instructions applicable to pre-filled syringes

Glass pre-filled syringes

- Prior to use, the pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.
- Remove tip cap by slowly turning the cap counterclockwise. Do not shake. Attach a needle appropriate for intramuscular injection and administer the entire volume.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection Children 5 to 11 years COVID-19 mRNA Vaccine raxtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Omicron XBB.1.5 is and what it is used for
2. What you need to know before your child receives Comirnaty Omicron XBB.1.5
3. How Comirnaty Omicron XBB.1.5 is given
4. Possible side effects
5. How to store Comirnaty Omicron XBB.1.5
6. Contents of the pack and other information

1. What Comirnaty Omicron XBB.1.5 is and what it is used for

Comirnaty Omicron XBB.1.5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Omicron XBB.1.5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Omicron XBB.1.5

Comirnaty Omicron XBB.1.5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Omicron XBB.1.5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty Omicron XBB.1.5 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty Omicron XBB.1.5. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Omicron XBB.1.5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Omicron XBB.1.5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Omicron XBB.1.5 is given

Comirnaty Omicron XBB.1.5 is given after dilution as an injection of 0.2 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty Omicron XBB.1.5 until at least 3 months after the most recent dose.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty Omicron XBB.1.5.

If you have any further questions on the use of Comirnaty Omicron XBB.1.5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Omicron XBB.1.5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Omicron XBB.1.5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Omicron XBB.1.5 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called raxtozinameran. After dilution, the vial contains 10 doses of 0.2 mL with 10 micrograms raxtozinameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty Omicron XBB.1.5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and an orange flip-off plastic cap with aluminium seal.

Pack size: 10 vials

Marketing Authorisation Holder

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Fax: +49 6131 9084-2121
service@biontech.de

Manufacturers

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Pfizer Manufacturing Belgium NV
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Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Tél/Tel: +32 (0)2 554 62 11
- **България:** Пфайзер Люксембург САРЛ, Клон, България, Тел: +359 2 970 4333
- **Česká republika:** Pfizer, spol. s r.o., Tel: +420 283 004 111
- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
- **Deutschland:** BioNTech Manufacturing GmbH, Tel: +49 6131 90840
- **Eesti:** Pfizer Luxembourg SARL Eesti filiaal, Tel: +372 666 7500

- **Ελλάδα:** Pfizer Ελλάς Α.Ε., Τηλ.: +30 210 6785 800
- **España:** Pfizer, S.L., Tel: +34914909900
- **France:** Pfizer, Tél +33 1 58 07 34 40
- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
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- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty Omicron XBB.1.5 intramuscularly after dilution as a single dose of 0.2 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has an **orange plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 ml doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty Omicron XBB.1.5 for children aged 5 to 11 years. **Low dead-volume syringes and/or needles** should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection Children 5 to 11 years COVID-19 mRNA Vaccine raxtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Omicron XBB.1.5 is and what it is used for
2. What you need to know before your child receives Comirnaty Omicron XBB.1.5
3. How Comirnaty Omicron XBB.1.5 is given
4. Possible side effects
5. How to store Comirnaty Omicron XBB.1.5
6. Contents of the pack and other information

1. What Comirnaty Omicron XBB.1.5 is and what it is used for

Comirnaty Omicron XBB.1.5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Omicron XBB.1.5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Omicron XBB.1.5

Comirnaty Omicron XBB.1.5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Omicron XBB.1.5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty Omicron XBB.1.5 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty Omicron XBB.1.5. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Omicron XBB.1.5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Omicron XBB.1.5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Omicron XBB.1.5 is given

Comirnaty Omicron XBB.1.5 is given as an injection of 0.3 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty Omicron XBB.1.5 until at least 3 months after the most recent dose.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty Omicron XBB.1.5.

If you have any further questions on the use of Comirnaty Omicron XBB.1.5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Omicron XBB.1.5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Omicron XBB.1.5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Single dose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Omicron XBB.1.5 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called raxtozinameran.
 - A single dose vial contains 1 dose of 0.3 mL with 10 micrograms of raxtozinameran per dose.
 - A multidose vial contains 6 doses of 0.3 mL with 10 micrograms of raxtozinameran per dose.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty Omicron XBB.1.5 looks like and contents of the pack

The vaccine is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal.

Single dose vials pack size: 10 vials

Multidose vials pack size: 10 vials

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturers

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- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
- **Deutschland:** BioNTech Manufacturing GmbH, Tel: +49 6131 90840
- **Eesti:** Pfizer Luxembourg SARL Eesti filiaal, Tel: +372 666 7500
- **Ελλάδα:** Pfizer Ελλάς Α.Ε., Τηλ.: +30 210 6785 800
- **España:** Pfizer, S.L., Tel: +34914909900
- **France:** Pfizer, Tél +33 1 58 07 34 40
- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
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- **Ísland:** Icepharma hf, Simi: +354 540 8000
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- **Κύπρος:** Pfizer Ελλάς Α.Ε. (Cyprus Branch), Τηλ: +357 22 817690
- **Latvija:** Pfizer Luxembourg SARL filiāle Latvijā, Tel.: +371 670 35 775
- **Lietuva:** Pfizer Luxembourg SARL filialas Lietuvoje, Tel. +370 52 51 4000
- **Magyarország:** Pfizer Kft, Tel: +36 1 488 3700
- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty Omicron XBB.1.5 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **blue plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty Omicron XBB.1.5 for children aged 5 to 11 years.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.

- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection Infants and children 6 months to 4 years COVID-19 mRNA Vaccine raxtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Omicron XBB.1.5 is and what it is used for
2. What you need to know before your child receives Comirnaty Omicron XBB.1.5
3. How Comirnaty Omicron XBB.1.5 is given
4. Possible side effects
5. How to store Comirnaty Omicron XBB.1.5
6. Contents of the pack and other information

1. What Comirnaty Omicron XBB.1.5 is and what it is used for

Comirnaty Omicron XBB.1.5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection is given to infants and children from 6 months to 4 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Omicron XBB.1.5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Omicron XBB.1.5

Comirnaty Omicron XBB.1.5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Omicron XBB.1.5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection is not recommended for children aged 5 years to 11 years.

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Omicron XBB.1.5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Package Leaflet for those formulations.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Omicron XBB.1.5 is given

If your infant is from 6 months to less than 12 months of age, he/she will be given Comirnaty Omicron XBB.1.5 with a **maroon cap** after dilution as an injection of **0.2 mL** into a muscle of the thigh. If your infant or child is 1 year of age or older, he/she will be given Comirnaty Omicron XBB.1.5 with a

maroon cap after dilution as an injection of **0.2 mL** into a muscle of the thigh or into a muscle of the upper arm.

If your child has not completed a COVID-19 primary vaccination course or has not been infected by COVID-19 in the past, your child will receive a maximum of 3 injections (the total number of doses required as primary course). It is recommended to receive the second dose 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If your child has previously completed a COVID-19 primary vaccination course or has had COVID-19, your child will receive 1 injection. If your child was previously vaccinated with a COVID-19 vaccine, your child should not receive a dose of Comirnaty Omicron XBB.1.5 until at least 3 months after the most recent dose.

If your child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty Omicron XBB.1.5.

Interchangeability

Your child may receive any previous or current Comirnaty vaccine for the primary course. Your child should not receive more than the total number of doses needed as primary course. Your child should only be administered the primary course once.

If you have any further questions on the use of Comirnaty Omicron XBB.1.5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Omicron XBB.1.5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- irritability (6 months to < 2 years)
- injection site: pain/tenderness, swelling
- tiredness, headache
- drowsiness (6 months to < 2 years)
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 6 months to 11 years)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash ('common' for 6 months to < 2 years) or itching
- decreased appetite ('very common' for 6 months to < 2 years)
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoaesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Omicron XBB.1.5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Omicron XBB.1.5 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called raxtozinameran. After dilution, the vial with a **maroon cap** contains **10 doses of 0.2 mL** with 3 micrograms raxtozinameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty Omicron XBB.1.5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of **10 doses** in a 2 mL clear vial (type I glass), with a rubber stopper and a **maroon flip-off plastic cap** with aluminium seal.

Pack size: 10 vials

Marketing Authorisation Holder

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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- **France:** Pfizer, Tél +33 1 58 07 34 40
- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
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- **Italia:** Pfizer S.r.l., Tel: +39 06 33 18 21
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- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

If the child has not completed a COVID-19 primary vaccination course or does not have a history of prior SARS-CoV-2 infection, administer Comirnaty Omicron XBB.1.5 with a **maroon cap** intramuscularly after dilution as a primary course of maximum 3 doses (the total number of doses

required as primary course); the second dose administered 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If the child has completed a COVID-19 primary vaccination course or has a history of prior SARS-CoV-2 infection, administer Comirnaty Omicron XBB.1.5 with a **maroon cap** intramuscularly after dilution a single dose of **0.2 mL**. If the individual was previously vaccinated with a COVID-19 vaccine, the individual should receive a dose of Comirnaty Omicron XBB.1.5 at least 3 months after the most recent dose.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label, or a different cap colour, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution for a vial with a maroon cap

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial **with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses using a vial with a maroon cap

- After dilution, the vial contains 2.6 mL from which **10 doses of 0.2 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw **0.2 mL** of Comirnaty Omicron XBB.1.5 for infants and children aged 6 months to 4 years.

Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.

- Each dose must contain **0.2 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.2 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection Infants and children 6 months to 4 years COVID-19 mRNA Vaccine raxtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Omicron XBB.1.5 is and what it is used for
2. What you need to know before your child receives Comirnaty Omicron XBB.1.5
3. How Comirnaty Omicron XBB.1.5 is given
4. Possible side effects
5. How to store Comirnaty Omicron XBB.1.5
6. Contents of the pack and other information

1. What Comirnaty Omicron XBB.1.5 is and what it is used for

Comirnaty Omicron XBB.1.5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection is given to infants and children from 6 months to 4 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Omicron XBB.1.5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Omicron XBB.1.5

Comirnaty Omicron XBB.1.5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Omicron XBB.1.5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection is not recommended for children aged 5 years to 11 years.

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Omicron XBB.1.5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Package Leaflet for those formulations.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Omicron XBB.1.5 is given

If your infant is from 6 months to less than 12 months of age, he/she will be given Comirnaty Omicron XBB.1.5 with a **yellow cap** after dilution as an injection of **0.3 mL** into a muscle of the thigh. If your infant or child is 1 year of age or older, he/she will be given Comirnaty Omicron XBB.1.5 with a

yellow cap after dilution as an injection of **0.3 mL** into a muscle of the thigh or into a muscle of the upper arm.

If your child has not completed a COVID-19 primary vaccination course or has not been infected by COVID-19 in the past, your child will receive a maximum of 3 injections (the total number of doses required as primary course). It is recommended to receive the second dose 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If your child has previously completed a COVID-19 primary vaccination course or has had COVID-19, your child will receive 1 injection. If your child was previously vaccinated with a COVID-19 vaccine, your child should not receive a dose of Comirnaty Omicron XBB.1.5 until at least 3 months after the most recent dose.

If your child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty Omicron XBB.1.5.

Interchangeability

Your child may receive any previous or current Comirnaty vaccine for the primary course. Your child should not receive more than the total number of doses needed as primary course. Your child should only be administered the primary course once.

If you have any further questions on the use of Comirnaty Omicron XBB.1.5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Omicron XBB.1.5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- irritability (6 months to < 2 years)
- injection site: pain/tenderness, swelling
- tiredness, headache
- drowsiness (6 months to < 2 years)
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 6 months to 11 years)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash ('common' for 6 months to < 2 years) or itching
- decreased appetite ('very common' for 6 months to < 2 years)
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoaesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Omicron XBB.1.5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Omicron XBB.1.5 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called raxtozinameran. After dilution, the vial with a **yellow cap** contains **3 doses** of **0.3 mL** with 3 micrograms raxtozinameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty Omicron XBB.1.5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of **3 doses** in a 2 mL clear vial (type I glass), with a rubber stopper and a **yellow flip-off plastic cap** with aluminium seal.

Pack size: 10 vials

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This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

If the child has not completed a COVID-19 primary vaccination course or does not have a history of prior SARS-CoV-2 infection, administer Comirnaty Omicron XBB.1.5 with a **yellow cap** intramuscularly after dilution as a primary course of maximum 3 doses (the total number of doses

required as primary course); the second dose administered 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If the child has completed a COVID-19 primary vaccination course or has a history of prior SARS-CoV-2 infection, administer Comirnaty Omicron XBB.1.5 with a **yellow cap** intramuscularly after dilution a single dose of **0.3 mL**. If the individual was previously vaccinated with a COVID-19 vaccine, the individual should receive a dose of Comirnaty Omicron XBB.1.5 at least 3 months after the most recent dose.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **yellow plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label or a different cap colour, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution for a vial with a yellow cap

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial **with 1.1 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.1 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.3 mL doses using a vial with a yellow cap

- After dilution, the vial contains 1.58 mL from which **3 doses** of **0.3 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw **0.3 mL** of Comirnaty Omicron XBB.1.5 for infants and children aged 6 months to 4 years. **Standard syringes and/or needles** can be used in order to extract 3 doses from a single vial.

- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty JN.1 30 micrograms/dose dispersion for injection Adults and adolescents from 12 years COVID-19 mRNA Vaccine bretovameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty JN.1 is and what it is used for
2. What you need to know before you receive Comirnaty JN.1
3. How Comirnaty JN.1 is given
4. Possible side effects
5. How to store Comirnaty JN.1
6. Contents of the pack and other information

1. What Comirnaty JN.1 is and what it is used for

Comirnaty JN.1 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty JN.1 30 micrograms/dose dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty JN.1 does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty JN.1

Comirnaty JN.1 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.

- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty JN.1 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty JN.1 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty JN.1. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty JN.1 30 micrograms/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty JN.1

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Comirnaty JN.1 may be given at the same time as a flu vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty JN.1 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty JN.1 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty JN.1 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty JN.1 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty JN.1 is given

Comirnaty JN.1 is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty JN.1 until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty JN.1.

If you have any further questions on the use of Comirnaty JN.1, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty JN.1 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty JN.1

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Single dose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty JN.1 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called bretovameran.
 - A single dose vial contains 1 dose of 0.3 mL with 30 micrograms bretovameran each.
 - A multidose vial contains 6 doses of 0.3 mL with 30 micrograms bretovameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty JN.1 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal.

Single dose vials pack size: 10 vials

Multidose vials pack size: 10 vials

Not all pack sizes may be marketed.

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- **España:** Pfizer, S.L., Tel: +34914909900
- **France:** Pfizer, Tél +33 1 58 07 34 40
- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
- **Ireland:** Pfizer Healthcare Ireland, Tel: 1800 633 363 (toll free), +44 (0)1304 616161
- **Ísland:** Icepharma hf, Simi: +354 540 8000
- **Italia:** Pfizer S.r.l., Tel: +39 06 33 18 21
- **Κύπρος:** Pfizer Ελλάς Α.Ε. (Cyprus Branch), Τηλ: +357 22 817690
- **Latvija:** Pfizer Luxembourg SARL filiāle Latvijā, Tel.: +371 670 35 775
- **Lietuva:** Pfizer Luxembourg SARL filialas Lietuvoje, Tel. +370 52 51 4000
- **Magyarország:** Pfizer Kft, Tel: +36 1 488 3700
- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
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- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Administer Comirnaty JN.1 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty JN.1 30 micrograms/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty JN.1.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty JN.1 30 micrograms/dose dispersion for injection in pre-filled syringe (plastic) Adults and adolescents from 12 years COVID-19 mRNA Vaccine bretovameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty JN.1 is and what it is used for
2. What you need to know before you receive Comirnaty JN.1
3. How Comirnaty JN.1 is given
4. Possible side effects
5. How to store Comirnaty JN.1
6. Contents of the pack and other information

1. What Comirnaty JN.1 is and what it is used for

Comirnaty JN.1 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty JN.1 30 micrograms/dose dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty JN.1 does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty JN.1

Comirnaty JN.1 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.

- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty JN.1 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty JN.1 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty JN.1. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty JN.1 30 micrograms/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty JN.1

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Comirnaty JN.1 may be given at the same time as a flu vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty JN.1 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty JN.1 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty JN.1 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty JN.1 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty JN.1 is given

Comirnaty JN.1 is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty JN.1 until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty JN.1.

If you have any further questions on the use of Comirnaty JN.1, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty JN.1 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty JN.1

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Frozen plastic pre-filled syringes: Must be thawed prior to use. A 10 pre-filled syringe pack can be thawed at 2 °C to 8 °C. It may take 2 hours to thaw. Ensure pre-filled syringes are completely thawed prior to use.

Alternatively, a 10 pre-filled syringe pack may be thawed for 60 minutes at room temperature (up to 30 °C).

If an individual pre-filled syringe is thawed outside the carton at room temperature (up to 30 °C), the pre-filled syringe must be used immediately.

Thawed (previously frozen) plastic pre-filled syringes: Once removed from the freezer, the pre-filled syringes can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). Upon moving the pre-filled syringes to 2 °C to 8 °C storage, update the expiry date on the carton. If received at 2 °C to 8 °C, check that the expiry date has been updated. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the thawed pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty JN.1 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called bretovameran.
 - Each pre-filled syringe contains 1 dose of 0.3 mL with 30 micrograms bretovameran.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty JN.1 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a pre-filled syringe (1 mL long cyclic-olefin copolymer plastic syringe) with plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber) without needle.

Pack size: 10 pre-filled syringes

Marketing Authorisation Holder

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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- **България:** Пфайзер Люксембург САРЛ, Клон, България, Тел: +359 2 970 4333
- **Česká republika:** Pfizer, spol. s r.o., Tel: +420 283 004 111
- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
- **Deutschland:** BioNTech Manufacturing GmbH, Tel: +49 6131 90840
- **Eesti:** Pfizer Luxembourg SARL Eesti filiaal, Tel: +372 666 7500

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- **Ireland:** Pfizer Healthcare Ireland, Tel: 1800 633 363 (toll free), +44 (0)1304 616161
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- **Κύπρος:** Pfizer Ελλάς Α.Ε. (Cyprus Branch), Τηλ: +357 22 817690
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- **Magyarország:** Pfizer Kft, Tel: +36 1 488 3700
- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
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- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
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- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
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- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty JN.1 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

Instructions applicable to pre-filled syringes

Plastic pre-filled syringe

- Frozen pre-filled syringes must be completely thawed prior to use.
 - A 10 pre-filled syringe pack can be thawed at 2 °C to 8 °C. It may take 2 hours to thaw.
 - Alternatively, a carton of 10 frozen pre-filled syringes may be thawed for 60 minutes at room temperature (up to 30 °C).
- If an individual pre-filled syringe is thawed outside the carton at room temperature (up to 30 °C), this must be used immediately.
- Upon moving the pre-filled syringes to 2 °C to 8 °C storage, update the expiry date on the carton. If received at 2 °C to 8 °C, check that the expiry date has been updated.
- Thawed (previously frozen) pre-filled syringes can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). Once thawed, the vaccine cannot be re-frozen.
- Prior to use, the thawed pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.
- Remove tip cap by slowly turning the cap counterclockwise. Do not shake. Attach a needle appropriate for intramuscular injection and administer the entire volume.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty JN.1 30 micrograms/dose dispersion for injection in pre-filled syringe (glass) Adults and adolescents from 12 years COVID-19 mRNA Vaccine bretovameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty JN.1 is and what it is used for
2. What you need to know before you receive Comirnaty JN.1
3. How Comirnaty JN.1 is given
4. Possible side effects
5. How to store Comirnaty JN.1
6. Contents of the pack and other information

1. What Comirnaty JN.1 is and what it is used for

Comirnaty JN.1 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty JN.1 30 micrograms/dose dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty JN.1 does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty JN.1

Comirnaty JN.1 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.

- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty JN.1 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty JN.1 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty JN.1. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty JN.1 30 micrograms/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty JN.1

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Comirnaty JN.1 may be given at the same time as a flu vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty JN.1 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty JN.1 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty JN.1 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty JN.1 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty JN.1 is given

Comirnaty JN.1 is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty JN.1 until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty JN.1.

If you have any further questions on the use of Comirnaty JN.1, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty JN.1 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the [national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty JN.1

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP.

Store at 2 °C to 8 °C. DO NOT FREEZE.

Store in the original package in order to protect from light.

The vaccine will be received and stored at 2 °C to 8 °C (refrigerated only). Prior to use, pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty JN.1 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called betovameran.
 - Each pre-filled syringe contains 1 dose of 0.3 mL with 30 micrograms betovameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol

- trometamol hydrochloride
- sucrose
- water for injections

What Comirnaty JN.1 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a pre-filled syringe (type I glass syringe) with plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber) without needle.

Pack size: 10 pre-filled syringes

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
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- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

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Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Administer Comirnaty JN.1 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

Instructions applicable to pre-filled syringes

Glass pre-filled syringes

- Prior to use, the pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.
- Remove tip cap by slowly turning the cap counterclockwise. Do not shake. Attach a needle appropriate for intramuscular injection and administer the entire volume.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection Children 5 to 11 years COVID-19 mRNA Vaccine bretovameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty JN.1 is and what it is used for
2. What you need to know before your child receives Comirnaty JN.1
3. How Comirnaty JN.1 is given
4. Possible side effects
5. How to store Comirnaty JN.1
6. Contents of the pack and other information

1. What Comirnaty JN.1 is and what it is used for

Comirnaty JN.1 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty JN.1 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty JN.1

Comirnaty JN.1 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty JN.1 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty JN.1 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty JN.1. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty JN.1

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

No data are available yet regarding the use of Comirnaty JN.1 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty JN.1 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty JN.1 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty JN.1 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty JN.1 is given

Comirnaty JN.1 is given after dilution as an injection of 0.2 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty JN.1 until at least 3 months after the most recent dose.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty JN.1.

If you have any further questions on the use of Comirnaty JN.1, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty JN.1 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty JN.1

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty JN.1 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called bretovameran. After dilution, the vial contains 10 doses of 0.2 mL with 10 micrograms bretovameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty JN.1 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and an orange flip-off plastic cap with aluminium seal.

Pack size: 10 vials

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Administer Comirnaty JN.1 intramuscularly after dilution as a single dose of 0.2 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- Verify that the vial has an **orange plastic cap** and the product **name is Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 ml doses

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty JN.1 for children aged 5 to 11 years.
Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty JN.1 10 micrograms/dose dispersion for injection Children 5 to 11 years COVID-19 mRNA Vaccine bretovameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty JN.1 is and what it is used for
2. What you need to know before your child receives Comirnaty JN.1
3. How Comirnaty JN.1 is given
4. Possible side effects
5. How to store Comirnaty JN.1
6. Contents of the pack and other information

1. What Comirnaty JN.1 is and what it is used for

Comirnaty JN.1 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty JN.1 10 micrograms/dose dispersion for injection is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty JN.1 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty JN.1

Comirnaty JN.1 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty JN.1 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty JN.1 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty JN.1. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty JN.1 10 micrograms/dose dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty JN.1

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

No data are available yet regarding the use of Comirnaty JN.1 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty JN.1 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty JN.1 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty JN.1 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty JN.1 is given

Comirnaty JN.1 is given as an injection of 0.3 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty JN.1 until at least 3 months after the most recent dose.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty JN.1.

If you have any further questions on the use of Comirnaty JN.1, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty JN.1 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty JN.1

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Single dose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty JN.1 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called bretovameran.
 - A single dose vial contains 1 dose of 0.3 mL with 10 micrograms of bretovameran per dose.
 - A multidose vial contains 6 doses of 0.3 mL with 10 micrograms of bretovameran per dose.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty JN.1 looks like and contents of the pack

The vaccine is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal.

Single dose vials pack size: 10 vials

Multidose vials pack size: 10 vials

Not all pack sizes may be marketed.

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- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
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- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Administer Comirnaty JN.1 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **blue plastic cap** and the product **name is Comirnaty JN.1 10 micrograms/dose dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty JN.1 for children aged 5 to 11 years.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection Infants and children 6 months to 4 years COVID-19 mRNA Vaccine bretovameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty JN.1 is and what it is used for
2. What you need to know before your child receives Comirnaty JN.1
3. How Comirnaty JN.1 is given
4. Possible side effects
5. How to store Comirnaty JN.1
6. Contents of the pack and other information

1. What Comirnaty JN.1 is and what it is used for

Comirnaty JN.1 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection is given to infants and children from 6 months to 4 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty JN.1 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty JN.1

Comirnaty JN.1 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty JN.1 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection is not recommended for children aged 5 years to 11 years.

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty JN.1

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Package Leaflet for those formulations.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty JN.1 is given

If your infant is from 6 months to less than 12 months of age, he/she will be given Comirnaty JN.1 with a **maroon cap** after dilution as an injection of **0.2 mL** into a muscle of the thigh. If your infant or child is 1 year of age or older, he/she will be given Comirnaty JN.1 with a **maroon cap** after dilution as an injection of **0.2 mL** into a muscle of the thigh or into a muscle of the upper arm.

If your child has not completed a COVID-19 primary vaccination course or has not been infected by COVID-19 in the past, your child will receive a maximum of 3 injections (the total number of doses required as primary course). It is recommended to receive the second dose 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If your child has previously completed a COVID-19 primary vaccination course or has had COVID-19, your child will receive 1 injection. If your child was previously vaccinated with a COVID-19 vaccine, your child should not receive a dose of Comirnaty JN.1 until at least 3 months after the most recent dose.

If your child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty JN.1.

Interchangeability

Your child may receive any previous or current Comirnaty vaccine for the primary course. Your child should not receive more than the total number of doses needed as primary course. Your child should only be administered the primary course once.

If you have any further questions on the use of Comirnaty JN.1, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty JN.1 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- irritability (6 months to < 2 years)
- injection site: pain/tenderness, swelling
- tiredness, headache
- drowsiness (6 months to < 2 years)
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 6 months to 11 years)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash ('common' for 6 months to < 2 years) or itching
- decreased appetite ('very common' for 6 months to < 2 years)
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty JN.1

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty JN.1 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called bretovameran. After dilution, the vial with a **maroon cap** contains **10 doses of 0.2 mL** with 3 micrograms bretovameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty JN.1 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of **10 doses** in a 2 mL clear vial (type I glass), with a rubber stopper and a **maroon flip-off plastic cap** with aluminium seal.

Pack size: 10 vials

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- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:

<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

If the child has not completed a COVID-19 primary vaccination course or does not have a history of prior SARS-CoV-2 infection, administer Comirnaty JN.1 with a **maroon cap** intramuscularly after dilution as a primary course of maximum 3 doses (the total number of doses required as primary course); the second dose administered 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If the child has completed a COVID-19 primary vaccination course or has a history of prior SARS-CoV-2 infection, administer Comirnaty JN.1 with a **maroon cap** intramuscularly after dilution a single dose of **0.2 mL**. If the individual was previously vaccinated with a COVID-19 vaccine, the individual should receive a dose of Comirnaty JN.1 at least 3 months after the most recent dose.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label, or a different cap colour, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution for a vial with a maroon cap

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial **with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses using a vial with a maroon cap

- After dilution, the vial contains 2.6 mL from which **10 doses** of **0.2 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw **0.2 mL** of Comirnaty JN.1 for infants and children aged 6 months to 4 years. **Low dead-volume syringes and/or needles** should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain **0.2 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.2 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection Infants and children 6 months to 4 years COVID-19 mRNA Vaccine bretovameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty JN.1 is and what it is used for
2. What you need to know before your child receives Comirnaty JN.1
3. How Comirnaty JN.1 is given
4. Possible side effects
5. How to store Comirnaty JN.1
6. Contents of the pack and other information

1. What Comirnaty JN.1 is and what it is used for

Comirnaty JN.1 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection is given to infants and children from 6 months to 4 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty JN.1 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty JN.1

Comirnaty JN.1 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty JN.1 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection is not recommended for children aged 5 years to 11 years.

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty JN.1

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Package Leaflet for those formulations.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty JN.1 is given

If your infant is from 6 months to less than 12 months of age, he/she will be given Comirnaty JN.1 with a **yellow cap** after dilution as an injection of **0.3 mL** into a muscle of the thigh. If your infant or child is 1 year of age or older, he/she will be given Comirnaty JN.1 with a **yellow cap** after dilution as an injection of **0.3 mL** into a muscle of the thigh or into a muscle of the upper arm.

If your child has not completed a COVID-19 primary vaccination course or has not been infected by COVID-19 in the past, your child will receive a maximum of 3 injections (the total number of doses required as primary course). It is recommended to receive the second dose 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If your child has previously completed a COVID-19 primary vaccination course or has had COVID-19, your child will receive 1 injection. If your child was previously vaccinated with a COVID-19 vaccine, your child should not receive a dose of Comirnaty JN.1 until at least 3 months after the most recent dose.

If your child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty JN.1.

Interchangeability

Your child may receive any previous or current Comirnaty vaccine for the primary course. Your child should not receive more than the total number of doses needed as primary course. Your child should only be administered the primary course once.

If you have any further questions on the use of Comirnaty JN.1, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty JN.1 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- irritability (6 months to < 2 years)
- injection site: pain/tenderness, swelling
- tiredness, headache
- drowsiness (6 months to < 2 years)
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 6 months to 11 years)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash ('common' for 6 months to < 2 years) or itching
- decreased appetite ('very common' for 6 months to < 2 years)
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty JN.1

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty JN.1 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called bretovameran. After dilution, the vial with a **yellow cap** contains **3 doses** of **0.3 mL** with 3 micrograms bretovameran each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty JN.1 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of **3 doses** in a 2 mL clear vial (type I glass), with a rubber stopper and a **yellow flip-off plastic cap** with aluminium seal.

Pack size: 10 vials

Marketing Authorisation Holder

BioNTech Manufacturing GmbH
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55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

Manufacturers

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Kupferbergterrasse 17 - 19
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Pfizer Manufacturing Belgium NV
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Puurs-Sint-Amands, 2870
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

- **België/Belgique/Belgien, Luxembourg/Luxemburg:** Pfizer S.A./N.V.,
Tél/Tel: +32 (0)2 554 62 11
- **България:** Пфайзер Люксембург САРЛ, Клон, България, Тел: +359 2 970 4333
- **Česká republika:** Pfizer, spol. s r.o., Tel: +420 283 004 111
- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
- **Deutschland:** BioNTech Manufacturing GmbH, Tel: +49 6131 90840

- **Eesti:** Pfizer Luxembourg SARL Eesti filiaal, Tel: +372 666 7500
- **Ελλάδα:** Pfizer Ελλάς Α.Ε., Τηλ.: +30 210 6785 800
- **España:** Pfizer, S.L., Tel: +34914909900
- **France:** Pfizer, Tél +33 1 58 07 34 40
- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
- **Ireland:** Pfizer Healthcare Ireland, Tel: 1800 633 363 (toll free), +44 (0)1304 616161
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- **Κύπρος:** Pfizer Ελλάς Α.Ε. (Cyprus Branch), Τηλ: +357 22 817690
- **Latvija:** Pfizer Luxembourg SARL filiāle Latvijā, Tel.: +371 670 35 775
- **Lietuva:** Pfizer Luxembourg SARL filialas Lietuvoje, Tel. +370 52 51 4000
- **Magyarország:** Pfizer Kft, Tel: +36 1 488 3700
- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:

<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

If the child has not completed a COVID-19 primary vaccination course or does not have a history of prior SARS-CoV-2 infection, administer Comirnaty JN.1 with a **yellow cap** intramuscularly after dilution as a primary course of maximum 3 doses (the total number of doses required as primary course); the second dose administered 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If the child has completed a COVID-19 primary vaccination course or has a history of prior SARS-CoV-2 infection, administer Comirnaty JN.1 with a **yellow cap** intramuscularly after dilution a single dose of **0.3 mL**. If the individual was previously vaccinated with a COVID-19 vaccine, the individual should receive a dose of Comirnaty JN.1 at least 3 months after the most recent dose.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- Verify that the vial has a **yellow plastic cap** and the product **name is Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label or a different cap colour, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution for a vial with a yellow cap

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial **with 1.1 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.1 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.3 mL doses using a vial with a yellow cap

- After dilution, the vial contains 1.58 mL from which **3 doses** of **0.3 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw **0.3 mL** of Comirnaty JN.1 for infants and children aged 6 months to 4 years. **Standard syringes and/or needles** can be used in order to extract 3 doses from a single vial.
- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty KP.2 30 micrograms/dose dispersion for injection Adults and adolescents from 12 years COVID-19 mRNA Vaccine mRNA encoding KP.2

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty KP.2 is and what it is used for
2. What you need to know before you receive Comirnaty KP.2
3. How Comirnaty KP.2 is given
4. Possible side effects
5. How to store Comirnaty KP.2
6. Contents of the pack and other information

1. What Comirnaty KP.2 is and what it is used for

Comirnaty KP.2 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty KP.2 30 micrograms/dose dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty KP.2 does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty KP.2

Comirnaty KP.2 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.

- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty KP.2 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty KP.2 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty KP.2. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty KP.2 30 micrograms/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty KP.2

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Comirnaty KP.2 may be given at the same time as a flu vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty KP.2 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty KP.2 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty KP.2 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty KP.2 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty KP.2 is given

Comirnaty KP.2 is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty KP.2 until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty KP.2.

If you have any further questions on the use of Comirnaty KP.2, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty KP.2 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the [national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty KP.2

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Single dose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty KP.2 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called mRNA encoding KP.2.
 - A single dose vial contains 1 dose of 0.3 mL with 30 micrograms mRNA encoding KP.2 each.
 - A multidose vial contains 6 doses of 0.3 mL with 30 micrograms mRNA encoding KP.2 each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty KP.2 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal.

Single dose vials pack size: 10 vials

Multidose vials pack size: 10 vials

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
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- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
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- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

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Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Administer Comirnaty KP.2 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty KP.2 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty KP.2 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty KP.2 30 micrograms/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty KP.2.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty KP.2 30 micrograms/dose dispersion for injection in pre-filled syringe (glass) Adults and adolescents from 12 years COVID-19 mRNA Vaccine mRNA encoding KP.2

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty KP.2 is and what it is used for
2. What you need to know before you receive Comirnaty KP.2
3. How Comirnaty KP.2 is given
4. Possible side effects
5. How to store Comirnaty KP.2
6. Contents of the pack and other information

1. What Comirnaty KP.2 is and what it is used for

Comirnaty KP.2 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty KP.2 30 micrograms/dose dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty KP.2 does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty KP.2

Comirnaty KP.2 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.

- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty KP.2 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty KP.2 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty KP.2. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty KP.2 30 micrograms/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty KP.2

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Comirnaty KP.2 may be given at the same time as a flu vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty KP.2 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty KP.2 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty KP.2 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty KP.2 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty KP.2 is given

Comirnaty KP.2 is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty KP.2 until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty KP.2.

If you have any further questions on the use of Comirnaty KP.2, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty KP.2 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the [national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty KP.2

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP.

Store at 2 °C to 8 °C. DO NOT FREEZE.

Store in the original package in order to protect from light.

The vaccine will be received and stored at 2 °C to 8 °C (refrigerated only). Prior to use, pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty KP.2 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called mRNA encoding KP.2.
 - Each pre-filled syringe contains 1 dose of 0.3 mL with 30 micrograms mRNA encoding KP.2 each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol

- trometamol hydrochloride
- sucrose
- water for injections

What Comirnaty KP.2 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a pre-filled syringe (type I glass syringe) with plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber) without needle.

Pack size: 10 pre-filled syringes

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- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
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Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Administer Comirnaty KP.2 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty KP.2 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty KP.2 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

Instructions applicable to pre-filled syringes

Glass pre-filled syringes

- Prior to use, the pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.
- Remove tip cap by slowly turning the cap counterclockwise. Do not shake. Attach a needle appropriate for intramuscular injection and administer the entire volume.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty KP.2 10 micrograms/dose dispersion for injection Children 5 to 11 years COVID-19 mRNA Vaccine mRNA encoding KP.2

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty KP.2 is and what it is used for
2. What you need to know before your child receives Comirnaty KP.2
3. How Comirnaty KP.2 is given
4. Possible side effects
5. How to store Comirnaty KP.2
6. Contents of the pack and other information

1. What Comirnaty KP.2 is and what it is used for

Comirnaty KP.2 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty KP.2 10 micrograms/dose dispersion for injection is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty KP.2 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty KP.2

Comirnaty KP.2 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty KP.2 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty KP.2 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty KP.2. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty KP.2 10 micrograms/dose dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty KP.2

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

No data are available yet regarding the use of Comirnaty KP.2 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty KP.2 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty KP.2 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty KP.2 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty KP.2 is given

Comirnaty KP.2 is given as an injection of 0.3 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty KP.2 until at least 3 months after the most recent dose.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty KP.2.

If you have any further questions on the use of Comirnaty KP.2, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty KP.2 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty KP.2

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Single dose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of single dose vials of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty KP.2 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called mRNA encoding KP.2.
 - A single dose vial contains 1 dose of 0.3 mL with 10 micrograms of mRNA encoding KP.2 per dose.
 - A multidose vial contains 6 doses of 0.3 mL with 10 micrograms of mRNA encoding KP.2 per dose.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty KP.2 looks like and contents of the pack

The vaccine is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal.

Single dose vials pack size: 10 vials

Multidose vials pack size: 10 vials

Not all pack sizes may be marketed.

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- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Administer Comirnaty KP.2 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty KP.2 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty KP.2 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **blue plastic cap** and the product **name is Comirnaty KP.2 10 micrograms/dose dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
 - Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
 - Single dose vials
 - Withdraw a single 0.3 mL dose of vaccine.
 - Discard vial and any excess volume.
 - Multidose vials
 - Multidose vials contain 6 doses of 0.3 mL each.
 - Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
 - Withdraw 0.3 mL of Comirnaty KP.2 for children aged 5 to 11 years.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty KP.2 3 micrograms/dose concentrate for dispersion for injection Infants and children 6 months to 4 years COVID-19 mRNA Vaccine mRNA encoding KP.2

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty KP.2 is and what it is used for
2. What you need to know before your child receives Comirnaty KP.2
3. How Comirnaty KP.2 is given
4. Possible side effects
5. How to store Comirnaty KP.2
6. Contents of the pack and other information

1. What Comirnaty KP.2 is and what it is used for

Comirnaty KP.2 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty KP.2 3 micrograms/dose concentrate for dispersion for injection is given to infants and children from 6 months to 4 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty KP.2 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty KP.2

Comirnaty KP.2 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty KP.2 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty KP.2 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty KP.2. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty KP.2 3 micrograms/dose concentrate for dispersion for injection is not recommended for children aged 5 years to 11 years.

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty KP.2

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

Comirnaty KP.2 3 micrograms/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the Package Leaflet for those formulations.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty KP.2 is given

If your infant is from 6 months to less than 12 months of age, he/she will be given Comirnaty KP.2 with a **yellow cap** after dilution as an injection of **0.3 mL** into a muscle of the thigh. If your infant or child is 1 year of age or older, he/she will be given Comirnaty KP.2 with a **yellow cap** after dilution as an injection of **0.3 mL** into a muscle of the thigh or into a muscle of the upper arm.

If your child has not completed a COVID-19 primary vaccination course or has not been infected by COVID-19 in the past, your child will receive a maximum of 3 injections (the total number of doses required as primary course). It is recommended to receive the second dose 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If your child has previously completed a COVID-19 primary vaccination course or has had COVID-19, your child will receive 1 injection. If your child was previously vaccinated with a COVID-19 vaccine, your child should not receive a dose of Comirnaty KP.2 until at least 3 months after the most recent dose.

If your child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty KP.2.

Interchangeability

Your child may receive any previous or current Comirnaty vaccine) for the primary course. Your child should not receive more than the total number of doses needed as primary course. Your child should only be administered the primary course once.

If you have any further questions on the use of Comirnaty KP.2, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty KP.2 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- irritability (6 months to < 2 years)
- injection site: pain/tenderness, swelling
- tiredness, headache
- drowsiness (6 months to < 2 years)
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 6 months to 11 years)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash ('common' for 6 months to < 2 years) or itching
- decreased appetite ('very common' for 6 months to < 2 years)
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty KP.2

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed (previously frozen) vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new expiry date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty KP.2 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called mRNA encoding KP.2. After dilution, the vial with a **yellow cap** contains **3 doses** of **0.3 mL** with 3 micrograms mRNA encoding KP.2 each.
- The other ingredients are:
 - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
 - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
 - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
 - cholesterol
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty KP.2 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of **3 doses** in a 2 mL clear vial (type I glass), with a rubber stopper and a **yellow flip-off plastic cap** with aluminium seal.

Pack size: 10 vials

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- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
- **Deutschland:** BioNTech Manufacturing GmbH, Tel: +49 6131 90840

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- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
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- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:

<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

If the child has not completed a COVID-19 primary vaccination course or does not have a history of prior SARS-CoV-2 infection, administer Comirnaty KP.2 intramuscularly after dilution as a primary course of maximum 3 doses (the total number of doses required as primary course); the second dose administered 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If the child has completed a COVID-19 primary vaccination course or has a history of prior SARS-CoV-2 infection, administer Comirnaty KP.2 intramuscularly after dilution a single dose of **0.3 mL**. If the individual was previously vaccinated with a COVID-19 vaccine, the individual should receive a dose of Comirnaty KP.2 at least 3 months after the most recent dose.

Additional doses may be given to individuals who are severely immunocompromised.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions prior to use

Comirnaty KP.2 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- Verify that the vial has a **yellow plastic cap** and the product **name is Comirnaty KP.2 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label or a different cap colour, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial **with 1.1 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.1 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.3 mL doses

- After dilution, the vial contains 1.58 mL from which **3 doses** of **0.3 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw **0.3 mL** of Comirnaty KP.2 for infants and children aged 6 months to 4 years. **Standard syringes and/or needles** can be used in order to extract 3 doses from a single vial.
- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.