10 November 2022
EMA/889536/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on extension of marketing authorisation

COMIRNATY

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005735/X/0147

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
BLA (US FDA)	Biologics License Application
BNT162b2 OMI	Omicron modified vaccine BNT162b2 OMICRON (B.1.1.529) BA.1
CDC (US)	Centers for Disease Control and Prevention
CFR	Case fatality rate
CI	confidence interval
CMC	chemistry, manufacturing and controls
CO	clinical overview
COVID-19	Coronavirus Disease 2019
CSR	clinical study report
EUA	Emergency Use Authorization
FDA (US)	Food and Drug Administration
GMR	geometric mean ratio
IM	intramuscularly
IND	Investigational New Drug application
LNP	lipid nanoparticle
modRNA	nucleoside-modified messenger RNA
mRNA	messenger RNA
P2 S	SARS-CoV-2 full-length, P2 mutant, “heads up,” prefusion spike glycoprotein
PI	Prescribing Information
RNA-LNP	ribonucleic acid
SAE	serious adverse event
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
sBLA	supplemental Biologics License Application
VOC	variant of concern

1. Background information on the procedure

1.1. Submission of the dossier

BioNTech Manufacturing GmbH submitted on 28 September 2022 an extension of the marketing authorisation.

Extension application to add a new strength of 5/5 µg/dose for the Comirnaty Original/Omicron BA.4-5 concentrate for dispersion for injection for children aged between 5 to 11 years.

The MAH applied for an addition of a new strength 5/5 micrograms/dose.

The MAH applied for the following indication for COMIRNATY the new strength:

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 who have previously received at least a primary vaccination course against COVID-19 (see sections 4.2 and 5.1).

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0466/2022 on the agreement of a paediatric investigation plan (PIP)

At the time of submission of the application, the PIP P/0466/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Menno van der Elst

The application was received by the EMA on	28 September 2022
The rolling review started on	29 September 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 October 2022
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	N/A
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	31 October 2022
BWP discussions took place on:	4 November 2022
ETF discussions took place on:	4 November 2022
The CHMP Rapporteurs circulated updated Joint Assessment Report	04 November 2022
The procedure started on (after administrative validation)	07 November 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to COMIRNATY on	10 November 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

COVID-19 is the respiratory disease caused by the coronavirus SARS-CoV2. The virus first emerged as a human pathogen in Wuhan province in China and has spread world-wide causing a pandemic. The WHO declared the COVID-19 outbreak as a pandemic in March 2020. The virus infects the airways and causes a broad spectrum of respiratory infection from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS).

The SARS-CoV-2 virus has repeatedly evolved and appeared in several variants causing new waves of infection. The variants have so far shown cross-reactivity with the original strain, which was the base for the currently approved vaccines. However, there is a concern that presently circulating virus variants are less cross-reactive with the original strain. The variant causing the latest waves of disease at the time of this application has been the Omicron variant, with several subvariants beginning with BA.1. Currently BA.5 is dominating in the EU.

2.1.2. Epidemiology and risk factors

All ages may present with the disease, but notably, case fatality rates (CFR) are elevated in persons >60 years of age. Comorbidities are also associated with increased CFR, including cardiovascular disease, diabetes, hypertension, and chronic respiratory disease. Healthcare workers are over-represented among COVID-19 patients due to occupational exposure to infected patients.

There are currently several vaccines approved for prevention of COVID-19 in adolescents, adults, elderly and children 5 to 11 years old. COVID-19 in children is mostly a mild disease although severe cases occur rarely, particularly in those with underlying, predisposing comorbidities.

Cumulatively, since the pandemic began, children represent about 1 in 5 reported cases in the US. Similarly, in Europe, COVID-19 cases surged the highest within the paediatric population <15 years of age during the Delta wave in July through September 2021, and also during the Omicron wave in January through March 2022. Although the severity of COVID-19 disease in children is substantially lower compared to adults, concerns have been raised that COVID-19 symptoms may be associated with more severe disease in children with chronic health conditions.

2.1.3. Biologic features

SARS-CoV-2 is an RNA virus with four structural proteins. One of them, the Spike protein is a surface protein which binds the angiotensin-converting enzyme 2 (ACE-2) present on host cells. Therefore, the Spike protein is considered a relevant antigen for vaccine development and is the main antigen in all currently developed vaccines against COVID-19.

While the efficacy of available vaccines, emulating the Wuhan strain, against severe disease appears largely retained, efficacy against symptomatic disease due to omicron variants is obviously reduced. Moreover, the duration of protection with the original may be reduced given that the emerging variant is less sensitive than the original target.

It is generally considered that protection may be optimised by a vaccine with a sequence that is as close to the circulating variant as possible. To optimize the broadness of the immune response to SARS-CoV-2 in the present situation, regulatory bodies (ICMRA) and WHO have suggested that a bivalent vaccine including both original as well as an omicron variant may be desirable.

2.1.4. Clinical presentation, diagnosis

COVID-19 presentation is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing. However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic patients, disease progression may lead to acute respiratory distress syndrome requiring ventilation, subsequent multi-organ failure, and death. COVID-19 caused by Omicron lineage generally presents with upper airways symptoms, cough and fever.

The United States Centers for Disease Control and Prevention (CDC) defined COVID 19 symptoms as including 1 or more of the following: 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, fatigue, headache, nasal congestion or runny nose, or nausea.

2.1.5. Management

Currently available therapies have different benefit-risk considerations depending on the stage of illness and disease manifestations. While care for individuals who have COVID-19 has improved with clinical experience, vaccination is the most effective medical countermeasure to decrease risk and mitigate spread of the SARS-CoV-2 virus during the ongoing pandemic. At this stage, there is no approved COVID-19 vaccine including BA.4-5 for children aged 5-<12 years of age.

2.2. About the product

Conditional marketing authorization was granted for Comirnaty 30 µg on 21 December 2020 for individuals ≥16 years of age and was later expanded on 28 May 2021 to include individuals ≥12 years of age. Comirnaty 10 µg for children 5-<12 years of age was approved in EU on 26 November 2021. Comirnaty Original/Omicron BA.1 (15+15µg) was approved 1 sept 2022 and Comirnaty Original/Omicron BA.4-5 (15+15µg) was approved 12 Sept 2022. Both bivalent vaccines are approved for participants ≥12 years of age. Comirnaty was granted the status of standard marketing authorisation on 10 October 2022.

The BNT162b2 Bivalent (BNT162b2 +BNT162b2 OMI BA.4/BA.5) variant vaccine (herein described to as Bivalent) is a preservative-free, sterile dispersion of lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer for IM administration. The BNT162b2 Bivalent vaccine 10 µg consists of nucleoside-modified messenger RNA (modRNA) encoding equal amounts of both a pre-fusion stabilized full-length variant of the SARS-CoV-2 S-glycoprotein (Original strain) and the Omicron BA.4 and BA.5 variant, 5 µg each. The BNT162b2 Bivalent drug product is formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4.

2.3. Quality aspects

2.3.1. Introduction

Pfizer and BioNTech have developed the Comirnaty vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus SARS-CoV-2. The vaccine is based on SARS CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs).

There are two approved formulations of Comirnaty vaccine:

- PBS/Sucrose finished product or *Comirnaty, 30 micrograms/dose, concentrate for dispersion for injection* which received a conditional approval 21 December 2020 (EMEA/H/C/005735)
- Tris/Sucrose finished product or *Comirnaty, 30 micrograms/dose, dispersion for injection*, approved 3 November 2021 (EMEA/H/C/005735/X/0044)

The primarily difference is the buffer used for finished product formulation and requirement for dilution prior to administration. The Tris/Sucrose finished product (Comirnaty dispersion for injection) is formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4 and is filled into vials at 2.25 mL fill volume, providing 6 doses of 30 µg RNA in 0.3 mL injection volume.

The emergence of SARS-CoV-2 variants with multiple mutations have led to development of variant vaccine constructs, specifically, the Omicron (BA.4/BA.5) as a variant of concern (VOC):

- Tris/Sucrose finished product, *Comirnaty Original/Omicron BA.4-5, (15/15 micrograms/dose, dispersion for injection*, approved 12 September 2022 (EMEA/H/C/005735/II/0143)

The bivalent vaccine is manufactured by mixing two active substance RNA constructs in an approximately 1:1 ratio prior to the lipid nanoparticle (LNP) formation and stabilization step. The bivalent finished product is formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4.

To assist in the public health crisis, a new paediatric 10 µg bivalent (Original/Omicron BA.4-5) finished product is being introduced in this line extension. Different dosage presentations for different age groups are already approved for the original Comirnaty vaccine which differ only in the fill volume and requirement for dilution prior to administration:

- *Comirnaty, 30 micrograms/dose, dispersion for injection*, approved 3 November 2021 (EMEA/H/C/005735/X/0044). The 30 µg RNA dosage presentation is filled at 2.25 mL per vial and is administered without dilution, providing 6 doses, each containing a 30 µg RNA dose in 0.3 mL injection volume for individuals 12+ years of age.
- *Comirnaty, 10 micrograms/dose, concentrate for dispersion for injection,* approved 26 November 2021 (EMEA/H/C/005735/X/0077). The 10 µg RNA dosage presentation is filled at 1.3 mL per vial and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses, each containing a 10 µg RNA dose in 0.2 mL injection volume for individuals 5 to <12 years of age.
- *Comirnaty, 3 micrograms/dose, concentrate for dispersion for injection,* approved 20 October 2022 (EMEA/H/C/005735/X/0138). The 3 µg RNA dosage presentation is filled at 0.4 mL per vial and requires dilution with 2.2 mL 0.9% sodium chloride prior to administration, providing 10 doses, each containing a 3 µg RNA dose in 0.2 mL injection volume for infants and children from 6 months to 4 years of age.
- *Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection,* approved 1 September 2022 (EMEA/H/C/005735/II/0140). This presentation is filled at 2.25 mL per vial and is administered without dilution, providing 6 doses, each containing a dose of 15 µg tozinameran and 15 µg riltozinameran in 0.3 mL injection volume for individuals 12+ years of age.
- *Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection,* approved 12 September 2022 (EMEA/H/C/005735/II/0140). This presentation is filled at 2.25 mL per vial and is administered without dilution, providing 6 doses, each containing a dose of 15 µg tozinameran and 15 µg famtozinameran in 0.3 mL injection volume for individuals 12+ years of age.

To support introduction of the 10 µg dose, this submission leverages the substantial supportive process and characterization information that was submitted for both the original Tris/Sucrose and bivalent finished products in prior variations, while also providing content specifically supporting introduction of the 10 µg dose.

- *Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection* is the subject of this procedure (EMEA/H/C/005735/II/0147). is filled at 1.3 mL per vial and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses, each containing a 5 µg tozinameran and 5 µg famtozinameran in 0.2 mL injection volume for individuals 5 to <12 years of age.

2.3.2. Active Substance

The active substances tozinameran and famtozinameran are already approved for the original Comirnaty vaccine formulations (EU/1/20/1528/001-010). No changes to the information are proposed.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and Pharmaceutical Development

The bivalent vaccine finished product 10 µg RNA dose is a preservative-free, sterile dispersion of RNA-containing lipid nanoparticles in an aqueous cryoprotectant buffer for intramuscular administration. The bivalent finished product is formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4 and contains an approximate 1:1 ratio of the original and omicron (BA.4/BA.5) variant strains. The bivalent finished product is filled at 1.3 mL fill volume, requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses, each a 10 µg RNA dose in 0.2 mL injection volume. Each strain, original and omicron (BA.4/BA.5), is present at approximately 5 µg/dose.

The qualitative and quantitative composition is provided in Table P.1-1.

Table P.1-1. Composition of Bivalent Finished Product, 10 µg RNA dose in 0.2 mL Injection Volume, 10 Dose Multi-dose Vials

Name of Ingredients	Reference to Standard	Function	Concentration Prior to Dilution (mg/mL)	Amount per vial after dilution[a,b]	Amount per dose
BNT162b2 (Original) drug substance (Construct 1)	In-house specification	Active ingredient	0.05	65 µg	5 µg
BNT162b2 Omicron (BA.4/BA.5) drug substance (Construct 2)	In-house specification	Active ingredient	0.05	65 µg	5 µg
ALC-0315	In-house specification	Functional lipid	1.43	1.86 mg	0.14 mg
ALC-0159	In-house specification	Functional lipid	0.18	0.23 mg	0.02 mg
DSPC	In-house specification	Structural lipid	0.31	0.40 mg	0.03 mg
Cholesterol	Ph. Eur.	Structural lipid	0.62	0.81 mg	0.06 mg
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103	133.9 mg	10.3 mg
Tromethamine (Tris base)[c]	USP-NF, Ph. Eur.	Buffer component	0.20	0.26 mg	0.02 mg
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)[d]	In-house specification	Buffer component	1.32	1.71 mg	0.13 mg
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.
Processing Aids/Residues[e]					
Ethanol	Ph. Eur.	Processing aid	N/A		
Citric acid monohydrate	Ph. Eur.	Processing aid			
Sodium citrate	Ph. Eur.	Processing aid			
Sodium hydroxide	Ph. Eur.	Processing aid			
HEPES	In-house specification	Drug substance buffer component			
EDTA	Ph. Eur., USP-NF	Drug substance buffer component			

All excipients except the functional lipids ALC-0315 and ALC-0159, the structural lipid DSPC and the buffer component TRIS HCl comply to Ph. Eur. grade. The functional lipids ALC-0315 and ALC-0159, the structural lipid DSPC and the buffer component TRIS HCl are all used in the currently approved Tris/Sucrose and PBS/Sucrose finished products of Comirnaty.

The container closure system is a 2 mL Type I borosilicate or aluminosilicate glass vial and a 13 mm bromobutyl rubber stopper and is the same container closure system as for the already approved Tris/Sucrose finished product of Comirnaty.

The processing aids and active substance formulation buffer components are residues that are essentially removed through the manufacturing process and are not considered as ingredients (excipients).

Pharmaceutical Development

The section has been updated in this Line extension application (EMEA/H/C/005735/X/0147) compared to the already approved procedures EMEA/H/C/005735/X/0077 and EMEA/H/C/005735/II/0143.

A revised QTPP has been developed for the bivalent vaccine to include the bivalent 10 µg presentation. No changes have been made compared to the QTPP for the original vaccine in Tris/Sucrose formulation except for a reflection of the use of two strains of mRNA, the inclusion of RNA ratio as a quality attribute and that the claimed shelf-life is 12 months.

No change in physicochemical properties, processability and stability is expected for the bivalent vaccine compared to the original vaccine in the Tris/Sucrose formulation.

The section on manufacturing process development and characterization has been updated to include vial content specification of 1.3 mL fill volume for the bivalent 10 µg presentation.

Comparability

Comparability has previously been acceptably demonstrated between clinical and commercial scale original finished product, between various manufacturing sites and between the PBS/Sucrose finished product and Tris/Sucrose finished product via comprehensive studies including both release testing and extended characterization testing. Due to the application of the same formulation, manufacturing process, and the use of the same manufacturing sites as the original finished product, extensive prior experience is leveraged, and it is found acceptable and sufficient that comparability has been established between the bivalent vaccine finished product to the original finished product based on an evaluation of release testing results against the acceptance criteria in the finished product specification.

For the bivalent 10 µg presentation of finished product, batch analysis data are provided in section 3.2.P.5.4 for the batches manufactured to date.

In conclusion, the information provided in section 3.2.P.2 on Pharmaceutical development is found sufficient and acceptable.

2.3.3.2. Manufacture of the product and process controls

The bivalent BA.4-5 vaccine (5/5 micrograms)/dose is manufactured at the same manufacturing sites, and using the same platform process, as currently approved Comirnaty vaccines (Tris/Sucrose formulation) (EU/1/20/1528/002-010). The GMP compliance of these sites has been previously confirmed.

The manufacturing process consists of four major manufacturing steps – LNP fabrication, bulk finished product formation, sterile filtration and aseptic filling. The manufacturing process is the same as for the bivalent BA.4-5 vaccine (15/15 micrograms)/dose (EMEA/H/C/005735/II/0143) except for a different fill volume. The commercial batch size is XX L of finished product solution corresponding to a maximum of approximately XX vials at 1.3 mL fill volume. The manufacturing process is sufficiently described, and suitable in-process controls (IPCs) are applied.

No process validation is performed for the bivalent BA.4-5 vaccine (5/5 micrograms)/dose. This is found acceptable since this line extension is a combination of the approved vaccines Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose and Comirnaty 10 microgram/dose.

2.3.3.3. Product specification, analytical procedures, batch analysis

The finished product specifications for the bivalent vaccine finished product presented in Table P.5-1 include tests for tests for Appearance (Visual), Appearance (Visible Particulates), Subvisible Particles (Ph. Eur.), pH (Ph. Eur.), Osmolality (Osmometry), LNP Size (Dynamic Light Scattering), LNP Polydispersity (Dynamic Light Scattering), RNA Encapsulation (Fluorescence assay), RNA content (Fluorescence assay), RNA ratio (ddPCR), ALC-0315 content (HPLC-CAD, HPLC-ELSD), ALC-0159 content (HPLC-CAD, HPLC-ELSD), DSPC content (HPLC-CAD, HPLC-ELSD), Cholesterol content (HPLC-CAD, HPLC-ELSD), extractable volume (Ph. Eur.), Lipid identities (HPLC-CAD, HPLC-ELSD), Identity of encoded RNA sequence (ddPCR), Potency / in Vitro Expression (Cell-based flow cytometry), RNA Integrity (Capillary Gel Electrophoresis), Bacterial Endotoxin (Ph. Eur.), Sterility (Ph. Eur.) and Container Closure Integrity (Dye incursion).

The specification includes a comprehensive set of relevant tests with corresponding acceptance criteria and are based on those established for the original finished product for the majority of the test attributes. The acceptance criteria for release and stability testing of the bivalent finished product are the same as for the original vaccine for all quality attributes except for the RNA ratio that is related to the mixing of the original and omicron (BA.4/BA.5) strains. In addition, the vial content (volume) acceptance criteria are updated to 1.3 mL fill volume for the bivalent 10 µg dose presentation as well as a new procedure number for subvisible particles is added.

Since the acceptance criteria for the bivalent vaccine finished product are based on the currently approved original vaccine finished product for the majority of test attributes, these acceptance criteria for test attributes are considered as clinically qualified to ensure quality, efficacy and safety.

The vial content (volume) for Tris/Sucrose finished product was determined to ensure that each 1.3 mL filled vial can deliver up to ten 10 µg doses of 0.2 mL each, following the addition of 1.3 mL 0.9% sodium chloride. The provided justification for vial content (volume) of 1.3 mL is found acceptable.

For the RNA ratio, a limit for the original and the omicron strains is proposed which, however, is not supported by the submitted batch data. No additional justification is provided. It is acknowledged that the experience is limited to a small number of finished product lots, manufactured from a limited number of active substance batches. Therefore, when a sufficient number of BNT162b2 Bivalent (Wildtype and Omicron) Finished Product batches are manufactured, the MAH will reassess the proposed specification for the RNA ratio by Q2 2023 as an outcome of variation EMEA/H/C/005735/II/0140 **(current REC 29)**. This is found acceptable.

Batch analysis data for the bivalent 10 µg vaccine finished product presentation have been provided for the four commercial scale batches GH9545, GH9702, GJ5342 and GK1657, all manufactured at Pfizer, Puurs. All results met the acceptance criteria at the time of release.

In addition, stability studies are ongoing for the commercial scale batches GH9545 and GK1657.

This is found acceptable.

2.3.3.4. Stability of the product

The proposed shelf-life for the bivalent vaccine finished product is 12 months when stored at the recommended storage temperature of -90 to -60°C, including short term storage at 5 ± 3°C for up to 10 weeks (within the 12-month shelf-life).

The proposed shelf-life is based on the shelf-life for the original Tris/Sucrose finished product, which is based on stability data obtained at the intended storage condition (-90 to -60°C) as well as the accelerated storage conditions (5 ± 3°C) during primary stability studies. Release data are available

for the bivalent finished product from the clinical lot 22-DP-01216 and the commercial scale confirmatory lot GH9545 and GK1657 at the intended storage condition (-90 to -60°C) as well as at the accelerated storage conditions (5 ± 3°C). These stability studies are currently on-going and data from these studies will be used to confirm the shelf-life of the bivalent finished product. The original Tris/Sucrose studies are also on-going and will be used to extend the shelf-life based on the acceptability of the data.

This approach to extrapolate the shelf-life from the already authorized original vaccine to the bivalent vaccine finished product is found acceptable since comparability has previously been acceptably demonstrated for a number of various comparisons of Comirnaty finished product such as between clinical and commercial scale original finished product, between various manufacturing sites and between the PBS/Sucrose finished product and the Tris/Sucrose finished product. Comparability has been demonstrated via comprehensive studies including both release testing and extended characterization testing. Due to the application of the same formulation, manufacturing process, and the use of the same manufacturing sites as the original finished product, extensive prior experience is leveraged for the bivalent finished product and comparability previously convincingly proven and concluded.

Therefore, the proposed shelf-life for the bivalent vaccine finished product of 12 months when stored at the recommended storage temperature of -90 to -60°C, including a short-term storage at 5 ± 3°C for up to 10 weeks (within the 12-month shelf-life). This is in-line with the wording in section 6.3 in the SmPC is agreed.

This is found acceptable.

2.3.3.5. Post approval change management protocol(s)

Not applicable.

2.3.3.6. Adventitious agents

The active substances (tozinameran and famtozinameran) are identical to that used for the currently approved Comirnaty vaccine formulations (EU/1/20/1528/001-010). Consequently, there are no changes to the active substance sections and full reference is made to the active substance data of Comirnaty, concentrate for dispersion for injection (EMEA/H/C/005735). Adequate testing for bioburden, endotoxins and sterility are also included at appropriate stages of the manufacturing process of the finished product.

2.3.3.7. GMO

Not applicable.

2.3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The MAH should reassess and optimise the proposed specification for the RNA ratio, when a sufficient number of BNT162b2 Bivalent (Wildtype and Omicron) Finished Product batches have been manufactured.

2.4. Non-clinical aspects

Not applicable

2.5. Clinical aspects

2.5.1. Introduction

No clinical studies including efficacy or immunogenicity were submitted in the current application concerning booster dose with Original/Omicron BA.4-5 (5/5) micrograms/dose for the age group 5-<12-year-old children.

Safety data have been submitted from study C4591044 cohort 2 in which 503 participants ≥12 years received either Original/BA.4-5 30µg or 60µg. Furthermore reference is made to study C4591031 Substudy D and E which included bivalent Original/BA.1 and was evaluated previously in EMEA/H/C/005735/II/0140. None of the studies include children aged 5-<12 years of age.

2.5.2. Clinical pharmacology

Not applicable

2.5.3. Clinical efficacy

The regulatory strategy proposed is to approve Original/Omicron BA.4-5 (5/5) micrograms/dose for the age group 5-<12-year-old children without efficacy data.

The efficacy was demonstrated for original Comirnaty vaccine, where the efficacy against COVID-19 is demonstrated for all age groups from 6 months old and upwards for primary series and for booster in 12 years old and upwards. Immunobridging has been accepted for the approval of booster dose of original Comirnaty 10 µg for 5-<12-year-olds (EMEA/H/C/005735/II/0129).

The approval of bivalent BA.1 and BA.4/5 in older age groups (at least 12 years and older) as a booster was based on immunogenicity data of bivalent variant-adapted vaccine Comirnaty Original/Omicron BA.1 (15/15) micrograms/dose (EMEA/H/C/005735/II/140). Original/Omicron BA.4/5 (15/15) (EMEA/H/C/005735/II/143) immunogenicity was extrapolated from a study with Comirnaty

Original/Omicron BA.1 (15/15) micrograms/dose. Study C4591044 which evaluates Original/Omicron BA.4/5 (15/15) is ongoing. Safety and immunogenicity (all participants) using validated BA.4/BA.5 neutralisation assay, are expected by December 2022/January 2023.

Efficacy of primary and booster doses of the original Comirnaty was demonstrated in clinical efficacy studies in participants from 12 years of age (2 doses + booster 30 µg), 5-<12 years of age (2 doses of 10 µg) and 6 months to 5 year of age (3 doses of 3 µg). In addition, immunogenicity data support the efficacy of a bivalent original/omicron BA.1 vaccine 15/15 µg, which has also been approved from 12 years of age. The bivalent Comirnaty Original/Omicron BA.1 vaccine induced superior antibody titres to BA.1 compared to the original Comirnaty, and non-inferior response to the Wuhan strain. No data of immunogenicity of Original/Omicron BA.1 among children below 12 years of age is available.

The MAH is planning extension of Study C4591048, which will study safety and immunogenicity of age-adapted Original/Omicron BA.4-5 among children 6 months to 12 years of age, as agreed in the PIP.

2.5.4. Discussion on clinical efficacy

Currently there are no immunogenicity or efficacy data of Original/Omicron BA.4-5, 5/5 µg as a booster dose among 5-<12-years-old children. These data are expected to be collected during study C4591048.

The bivalent Comirnaty Original/Omicron BA.1 vaccine induced superior antibody titres to BA.1 compared to the original Comirnaty, and non-inferior response to the Wuhan strain. No data of immunogenicity of Original/Omicron BA.1 among children below 12 years of age is available. It is anticipated that the updated bivalent variant vaccine Original/Omicron BA.4-5 is immunogenically superior to neutralise BA.4-5 and non-inferior to neutralise Wuhan in comparison to Original Comirnaty. Immunogenicity data to confirm this assumption are expected post-approval for persons 12 years of age and older from study C4591044 cohort 2. There is a planned extension of study C4591048 to evaluate immunogenicity of Original/BA.4-5 5/5 µg for 5-<12 year olds and 1.5/1.5 µg for 6 months to <5 age old groups (**REC**).

In addition, pre-clinical data support that the BA.5 variant-adapted mRNA can induce antibodies against omicron BA.5 (EMEA/H/C/005735/II/143).

2.5.5. Conclusions on the clinical efficacy

The bivalent Comirnaty Original/Omicron BA.1 vaccine induced superior antibody titres to BA.1 compared to the original Comirnaty, and non-inferior response to the Wuhan strain. It is anticipated that the updated bivalent variant vaccine Original/Omicron BA.4/5 is immunogenically superior to neutralise BA.4/5 and non-inferior to neutralise Wuhan in comparison to Original Comirnaty.

Pre-clinical data support that the BA.5 variant-adapted mRNA can induce antibodies against omicron BA.5.

The following measures are considered necessary to address issues related to efficacy: The delivery of immunogenicity and safety data from study C4591044 for age group 12-17 years of age and C4591048 for the age group between 5 – 11 years of age (**REC**).

2.5.6. Clinical safety

To support the inclusion of children aged 5-<12 years to receive a booster dose (dose 4) of the bivalent vaccine Original/ BA.4-5 5/5µg, the MAH has referred to study C4591031 Substudy D and E

which included bivalent Original/BA.1 and was evaluated previously in EMEA/H/C/005735/II/0140. Furthermore, 7-day post dose safety data from study C4591044 cohort 2 in which 503 participants ≥12 years received either Original/BA.4-5 30µg or 60µg, has been submitted. None of the studies includes children aged 5-<12 years of age.

In all studies, reactogenicity and antipyretic/pain medication use was recorded for 7 days after study vaccination using prompts from an electronic diary (e-diary). AEs were collected from the study vaccination up to 1 month after the study vaccination, and serious AEs (SAEs) were collected from study vaccination up to 6 months post-Dose. AEs are categorized by frequency, maximum severity, seriousness, and relationship to study intervention using system organ class (SOC) and preferred term (PT) according to MedDRA. Deaths are recorded to the end of study.

2.5.6.1. Study C4591044

2.5.6.1.1. Patient exposure

Study C4591044 is a randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of new bivalent vaccines. The study vaccine candidates are divided into cohorts, which may be studied in a staggered or parallel manner, as required by the clinical plan. The report submitted presents 7 days post-dose reactogenicity and AE data for 503 participants ≥12 years of age in Cohort 2 who received either 30 µg or 60 µg dose of BNT162b2 bivalent Original/BA.4-5 after receiving 3 doses of Original 30µg. At the cut-off 7 days after first dose, none of the participants has been excluded from the safety population.

The 503 participants were divided into three age groups that included about 100 participants each: 12-17 years, 18-55 years and >55 years of age. The participants aged 12-17 years received Original/BA.4-5 30 µg only, whereas the two older age groups received either Original/BA.4-5 30 µg or 60 µg as a fourth dose. All participants had previously received three doses of Comirnaty 30 µg, and a majority received their fourth dose ≥7 to ≤12 months after dose 3.

The disposition is illustrated in the table below.

Table 1: Disposition of All Participants – Cohort 2 – Randomised population

	Vaccine Group (as Randomized)					
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg			BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg		
	12-17 Years n[a] (%)	18-55 Years n[a] (%)	>55 Years n[a] (%)	18-55 Years n[a] (%)	>55 Years n[a] (%)	Total n[a] (%)
Randomized[b]	97 (100.0)	100 (100.0)	101 (100.0)	106 (100.0)	99 (100.0)	503 (100.0)
Not vaccinated	0	0	0	0	0	0
Vaccinated	97 (100.0)	100 (100.0)	101 (100.0)	106 (100.0)	99 (100.0)	503 (100.0)
Completed 7-day post–study vaccination visit	97 (100.0)	100 (100.0)	101 (100.0)	106 (100.0)	99 (100.0)	503 (100.0)
Withdrawn from the study	0	0	0	1 (0.9)	0	1 (0.2)
Reason for withdrawal						
Physician decision	0	0	0	1 (0.9)	0	1 (0.2)

a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 20SEP2022 (15:59) Source Data: adds Table Generation: 21SEP2022 (23:00) (Data cutoff date : 12SEP2022 Database snapshot date : 19SEP2022) Output File:

A non-study vaccine (meningococcal vaccine B) received within 28 days before study vaccination was received by 1 participant (1.0%) in the 12 to 17 years of age group who received a booster dose of BNT162b2 bivalent 30-µg. No participants received a non-study vaccine after study vaccination.

The demographics is illustrated in the table below.

Table 2: Demographic characteristics – Cohort 2 – Safety population

	Vaccine Group (as Administered)					
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg			BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg		
	12-17 Years (N[a]=97) n[b] (%)	18-55 Years (N[a]=100) n[b] (%)	>55 Years (N[a]=101) n[b] (%)	18-55 Years (N[a]=106) n[b] (%)	>55 Years (N[a]=99) n[b] (%)	Total (N[a]=503) n[b] (%)
Sex						
Male	52 (53.6)	42 (42.0)	64 (63.4)	44 (41.5)	46 (46.5)	248 (49.3)
Female	45 (46.4)	58 (58.0)	37 (36.6)	62 (58.5)	53 (53.5)	255 (50.7)
Race						
White	82 (84.5)	80 (80.0)	81 (80.2)	86 (81.1)	90 (90.9)	419 (83.3)
Black or African American	8 (8.2)	8 (8.0)	14 (13.9)	11 (10.4)	7 (7.1)	48 (9.5)
American Indian or Alaska Native	0	0	1 (1.0)	0	0	1 (0.2)
Asian	3 (3.1)	10 (10.0)	3 (3.0)	9 (8.5)	2 (2.0)	27 (5.4)
Native Hawaiian or other Pacific Islander	0	0	1 (1.0)	0	0	1 (0.2)
Multiracial	3 (3.1)	2 (2.0)	1 (1.0)	0	0	6 (1.2)
Not reported	1 (1.0)	0	0	0	0	1 (0.2)
Ethnicity						
Hispanic/Latino	7 (7.2)	11 (11.0)	10 (9.9)	15 (14.2)	11 (11.1)	54 (10.7)
Non-Hispanic/non-Latino	88 (90.7)	88 (88.0)	91 (90.1)	90 (84.9)	85 (85.9)	442 (87.9)
Not reported	2 (2.1)	1 (1.0)	0	1 (0.9)	3 (3.0)	7 (1.4)
Age at vaccination (years)						
Mean (SD)	15.1 (1.40)	39.4 (8.91)	65.8 (6.11)	39.8 (9.96)	64.0 (6.27)	44.9 (19.86)
Median	15.0	40.0	65.0	41.0	63.0	48.0
Min, max	(12, 17)	(19, 55)	(56, 79)	(18, 55)	(56, 85)	(12, 85)
Baseline SARS-CoV-2 status						
Positive[c]	67 (69.1)	63 (63.0)	59 (58.4)	78 (73.6)	61 (61.6)	328 (65.2)
Negative[d]	25 (25.8)	36 (36.0)	37 (36.6)	24 (22.6)	31 (31.3)	153 (30.4)
Missing	5 (5.2)	1 (1.0)	5 (5.0)	4 (3.8)	7 (7.1)	22 (4.4)
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (months)[e]						
n	97	100	101	106	99	503
Mean (SD)	8.4 (1.26)	10.6 (1.72)	10.6 (1.25)	10.6 (1.40)	10.7 (1.27)	10.2 (1.65)
Median	8.3	11.0	11.0	10.9	11.0	10.5
Min, max	(5.6, 12.0)	(5.6, 14.3)	(5.5, 13.0)	(6.6, 14.2)	(6.6, 13.0)	(5.5, 14.3)
≥5 to <7 Months	10 (10.3)	5 (5.0)	1 (1.0)	3 (2.8)	1 (1.0)	20 (4.0)
≥7 to <9 Months	70 (72.2)	10 (10.0)	9 (8.9)	9 (8.5)	9 (9.1)	107 (21.3)
≥9 to ≤12 Months	17 (17.5)	73 (73.0)	86 (85.1)	87 (82.1)	80 (80.8)	343 (68.2)
>12 Months[f]	0	12 (12.0)	5 (5.0)	7 (6.6)	9 (9.1)	33 (6.6)
Body mass index (BMI)						
Underweight (<18.5 kg/m^2)	17 (17.5)	1 (1.0)	3 (3.0)	6 (5.7)	1 (1.0)	28 (5.6)
Normal weight (≥18.5-24.9 kg/m^2)	60 (61.9)	41 (41.0)	28 (27.7)	27 (25.5)	21 (21.2)	177 (35.2)
Overweight (≥25.0-29.9 kg/m^2)	14 (14.4)	34 (34.0)	31 (30.7)	32 (30.2)	41 (41.4)	152 (30.2)
Obese (≥30.0 kg/m^2)	6 (6.2)	24 (24.0)	39 (38.6)	41 (38.7)	36 (36.4)	146 (29.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
d. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
e. For one participant who received a different COVID-19 vaccine in error, time was calculated from the last reported dose of COVID-19 vaccine.
f. Protocol-specified eligibility window for time since last BNT162b2 dose prior to study vaccination is 150-365 days. Some participants appear in ">12 months" row who
were eligible for inclusion in the study (last dose ≤365 days before vaccination), due to conversion factor of 28 days/month.
PFIZER CONFIDENTIAL SDTM Creation: 20SEP2022 (15:58) Source Data: adsl Table Generation: 22SEP2022 (05:05)
(Data cutoff date : 12SEP2022 Database snapshot date : 19SEP2022) Output File:
./nda2_ub1044/C4591044_7DPD_C2/adsl_s005_saf_c2

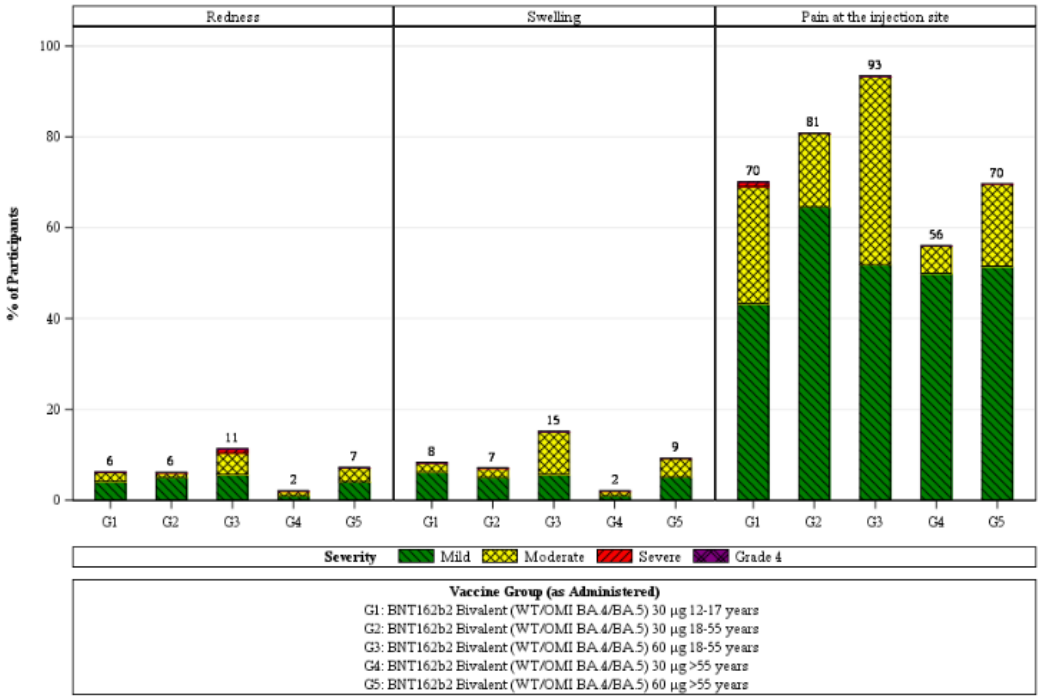
2.5.6.1.2. Adverse events

Reactogenicity study C4591044 – cohort 2

Local reactions

Most local reactions were mild or moderate in severity. Severe local reactions were reported by 1 (1.0%) participant in the 12 to 17 years of age group who received a booster dose of BNT162b2 bivalent 30-µg. No Grade 4 local reactions were reported in any group. The median onset for all local reactions was 1 to 2.5 days, and all events resolved within a median duration of 1 to 3 days after onset.

Figure 1: Local reactions, by maximum severity, within 7 days after the study vaccination – cohort 2 – safety population

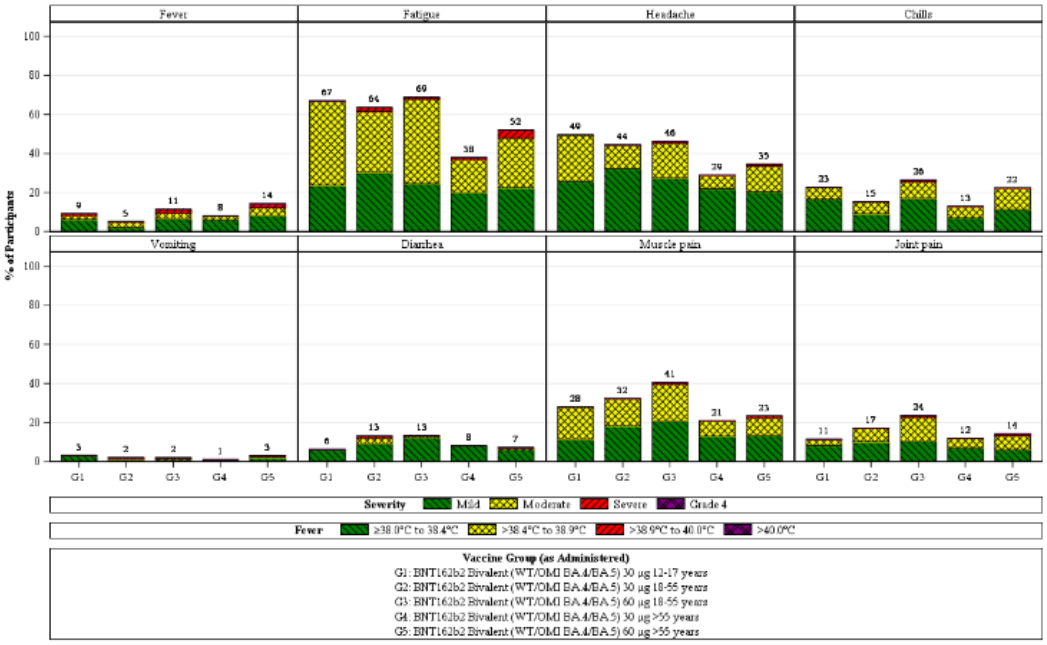


Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 20SEP2022 (15:59) Source Data: adfacevd Table Generation: 22SEP2022 (02:16)
(Data Cutoff Date: 12SEP2022, Database Snapshot Date: 19SEP2022) Output File: ./nda2_ub1044/C4591044_7DPD_C2/adce_f001_lr_c2

Systemic events

Most systemic events were mild or moderate in severity. In the BNT162b2 bivalent 30-µg dose group, severe systemic events of fever (n=1), fatigue (n=3), and diarrhoea (n=1) were reported. In the BNT162b2 bivalent 60-µg dose group, severe systemic events of fever (n=4), fatigue (n=5), headache (n=2), chills (n=1), muscle pain (n=2), and joint pain (n=2) were reported. No Grade 4 systemic events were reported in any group. The median onset for all systemic events was 2 to 4 days, and all events resolved within a median duration of 1 to 2 days after onset.

Figure 2: Systemic events, by maximum severity, within 7 days after the study vaccination – cohort 2 – safety population



Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 20SEP2022 (15:59) Source Data: adfacevd Table Generation: 22SEP2022 (02:16)
(Data Cutoff Date: 12SEP2022, Database Snapshot Date: 19SEP2022) Output File: /nda2_tib1044/C4591046_7DPD_C2/adce_f001_se_c2

Adverse events study C4591044 – cohort 2

An overview of AEs reported from study vaccination through 7 days after study vaccination is shown in the table below.

Table 3: Number (%) of participants reporting at least 1 adverse event from the study vaccination through 7 days after the study vaccination – Cohort 2 – Safety Population

	Vaccine Group (as Administered)				
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg			BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg	
	12-17 Years (N[a]=97)	18-55 Years (N[a]=100)	>55 Years (N[a]=101)	18-55 Years (N[a]=106)	>55 Years (N[a]=99)
Adverse Event	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any adverse event	5 (5.2)	0	1 (1.0)	1 (0.9)	2 (2.0)
Related[c]	5 (5.2)	0	0	1 (0.9)	1 (1.0)
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Any serious adverse event	0	0	0	0	0
Related[c]	0	0	0	0	0
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Any nonserious adverse event	5 (5.2)	0	1 (1.0)	1 (0.9)	2 (2.0)
Related[c]	5 (5.2)	0	0	1 (0.9)	1 (1.0)
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Any adverse event leading to withdrawal	0	0	0	0	0
Related[c]	0	0	0	0	0
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Death	0	0	0	0	0

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to study intervention.
PFIZER CONFIDENTIAL SDTM Creation: 20SEP2022 (15:58) Source Data: adae Table Generation: 23SEP2022 (13:24) (Data cutoff date : 12SEP2022 Database snapshot date : 19SEP2022) Output File: ./nda2 ub1044/C4591044 7DPD C2/adae 091 exp 1m sex

AEs reported from study vaccination through 7 days after study vaccination are presented by SOC/PT in the table below.

Table 4: Number (%) of participants reporting at least 1 adverse event from the study vaccination through 7 days after the study vaccination, by System Organ Class and Preferred Term – Cohort 2 – Safety Population

	Vaccine Group (as Administered)									
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg						BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg			
	12-17 Years (N[a]=97)		18-55 Years (N[a]=100)		>55 Years (N[a]=101)		18-55 Years (N[a]=106)		>55 Years (N[a]=99)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	5 (5.2)	(1.7, 11.6)	0	(0.0, 3.6)	1 (1.0)	(0.0, 5.4)	1 (0.9)	(0.0, 5.1)	2 (2.0)	(0.2, 7.1)
Blood and lymphatic system disorders	0	(0.0, 3.7)	0	(0.0, 3.6)	0	(0.0, 3.6)	1 (0.9)	(0.0, 5.1)	0	(0.0, 3.7)
Lymphadenopathy	0	(0.0, 3.7)	0	(0.0, 3.6)	0	(0.0, 3.6)	1 (0.9)	(0.0, 5.1)	0	(0.0, 3.7)
General disorders and administration site conditions	4 (4.1)	(1.1, 10.2)	0	(0.0, 3.6)	0	(0.0, 3.6)	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.5)
Fatigue	3 (3.1)	(0.6, 8.8)	0	(0.0, 3.6)	0	(0.0, 3.6)	0	(0.0, 3.4)	0	(0.0, 3.7)
Injection site pain	2 (2.1)	(0.3, 7.3)	0	(0.0, 3.6)	0	(0.0, 3.6)	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.5)
Chills	1 (1.0)	(0.0, 5.6)	0	(0.0, 3.6)	0	(0.0, 3.6)	0	(0.0, 3.4)	0	(0.0, 3.7)
Injection site erythema	1 (1.0)	(0.0, 5.6)	0	(0.0, 3.6)	0	(0.0, 3.6)	0	(0.0, 3.4)	0	(0.0, 3.7)
Injury, poisoning and procedural complications	0	(0.0, 3.7)	0	(0.0, 3.6)	0	(0.0, 3.6)	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.5)
Fall	0	(0.0, 3.7)	0	(0.0, 3.6)	0	(0.0, 3.6)	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.5)
Musculoskeletal and connective tissue disorders	2 (2.1)	(0.3, 7.3)	0	(0.0, 3.6)	1 (1.0)	(0.0, 5.4)	0	(0.0, 3.4)	0	(0.0, 3.7)
Myalgia	2 (2.1)	(0.3, 7.3)	0	(0.0, 3.6)	0	(0.0, 3.6)	0	(0.0, 3.4)	0	(0.0, 3.7)
Muscle spasms	0	(0.0, 3.7)	0	(0.0, 3.6)	1 (1.0)	(0.0, 5.4)	0	(0.0, 3.4)	0	(0.0, 3.7)
Nervous system disorders	1 (1.0)	(0.0, 5.6)	0	(0.0, 3.6)	0	(0.0, 3.6)	0	(0.0, 3.4)	0	(0.0, 3.7)
Headache	1 (1.0)	(0.0, 5.6)	0	(0.0, 3.6)	0	(0.0, 3.6)	0	(0.0, 3.4)	0	(0.0, 3.7)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 20SEP2022 (15:58) Source Data: adae Table Generation: 23SEP2022 (13:25)
(Data cutoff date : 12SEP2022 Database snapshot date : 19SEP2022) Output File: ./nda2_ub1044/C4591044_7DPD_C2/adae_130_exp_1m_sex

Reported AEs were overall consistent with reactogenicity events that were reported as AEs (e.g., fatigue, injection site pain or erythema, chills, headache, myalgia), and included lymphadenopathy which is recognized as a potentially vaccine-related event. Non-reactogenicity type events reported in 2 participants.

1. One event of a fall (accidental mechanical fall) was reported in an individual above 75 years of age considered by the investigator as not related to study intervention, and reported as resolved within 1 day after onset. No cause or further detail was specified.
2. One event of muscle spasm was reported in an individual above 70 years of age, considered by the investigator as not related to study intervention, and reported as resolved within 1 day after onset. No cause or further detail was specified.

Immediate Adverse Events

One (1.0%) participant in the 12 to 17 years of age group reported an immediate AE of injection site erythema within 30 minutes of study vaccination.

Related Adverse Events

Related AE's were reported by 7 participants and were consistent with reactogenicity events that were reported as AEs. Most related AEs were consistent with reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 5 participants. Additionally, 1 case of lymphadenopathy was reported by 1 participant in the 18 to 55 years of age group who received BNT162b2 60-µg dose.

2.5.6.1.3. Serious adverse event/deaths/other significant events

No deaths or SAEs were reported by participants in Cohort 2 from study vaccination through 7 days post vaccination.

2.5.6.1.4. Post marketing experience

Surveillance of BNT162b2 post-authorisation safety data has confirmed the overall favourable benefit-risk assessment of the vaccine.

No post-marketing data have been submitted for the bivalent Original/BA.4-5 vaccine.

2.5.6.2. C4591031 Substudy D and E

Safety results from participants >55 years of age in C4591031 Substudy E were previously assessed (EMEA/H/C/005735/II/0140). A brief summary of results is provided below:

Analysis of safety data from 1840 BNT162b2-experienced participants >55 years of age who received BNT162b2, BNT162b2 OMI or BNT162b2 + BNT162b2 OMI 30-µg or 60-µg dose level as a booster (Dose 4) did not identify any new safety-related concerns.

Reactogenicity was mostly mild to moderate and short-lived. Reactogenicity in participants who received a 30-µg dose level was lower, with mild to moderate injection site pain, fatigue and muscle pain less frequent compared to participants who received a 60-µg dose level. Fevers were reported infrequently.

The adverse event (AE) profile mostly reflected reactogenicity or age-related illnesses. The observed safety profile across age groups demonstrates a safe and tolerable vaccine, similar to the known safety profile of BNT162b2. From study vaccination to 1 month post-Dose, a similar proportion of participants across vaccine groups reported any AE (range: 3.6% to 10.4%), with AEs generally reported at similar frequencies in the vaccine groups, except for participants in the BNT162b2 OMI 30 µg and BNT162b2 +BNT162b2 OMI 60 µg groups who reported AEs more frequently (8.5% and 10.4%, respectively). Any severe or serious AEs (SAEs) were reported across vaccine groups by ≤0.9% and ≤1.0%, respectively. For participants in the bivalent BNT162b2 + BNT162b2 OMI 30 µg group, any AEs, severe AEs or SAEs were reported by 6.2%, 0.3%, and 0.3% of participants, respectively.

There were few AEs of clinical interest reported across all vaccine groups. Lymphadenopathy has been identified as an adverse reaction causally associated with the vaccine and has been observed during the two-dose primary series across age groups in these studies. These events are typically mild and self-limited. Incidence of lymphadenopathy in the expanded cohort of Substudy E (participants >55 years of age) was ≤1.0% (range: 0 to 1.0%) overall across the vaccine groups and 0.3% in bivalent BNT162b2 +BNT162b2 OMI 30 µg group. No cases of anaphylaxis, myocarditis/pericarditis, appendicitis, or Bell's Palsy were reported in any group over the course of at least 1 month of follow-up after vaccination in individuals >55 years of age.

Additional supportive safety data from approximately 640 participants ≥18 to ≤55 years of age in Study C4591031 Substudy D Cohort 2 who had a median of 1.4 months of follow-up after a booster dose (Dose 4) demonstrated that the tolerability and safety profile of monovalent BNT162b2 OMI 30 µg and BNT162b2 30 µg up to 1 month after Dose 4 vaccination (to the data cut-off date) was acceptable and consistent with results previously reported in clinical trials for BNT162b2 30 µg in this age group.

Table 5: Participants reporting local reactions and systemic events within 7 days post-dose 4 of BNT162b2, monovalent BNT162b2 OMI BA.1, bivalent BNT162b2 + BNT162b2 OMI BA.1 or bivalent BNT162b2 + BNT162b2 OMI BA.4/5 at 30 µg or 60µg dose level in studies C4591031 substudy D, E and C4591044 cohort 2

C4591031 Substudy D[a]		C4591031 Substudy E[b]			C4591044 Cohort 2[c]				
BNT162b2 OMI BA.1 30 µg	BNT162b2 30 µg	BNT162b2 30 µg	BNT162b2 OMI BA.1 30 µg	BNT162b2 + BNT162b2 OMI BA.1 30 µg	BNT162b2 Bivalent 30 µg (WT/OMI BA.4/BA.5)			BNT162b2 Bivalent 60 µg (WT/OMI BA.4/BA.5)	
(18 to 55 Years)		(>55 Years)			12-17 Y	18-55 Y	>55 Y	18-55 Y	>55 Y
(N=294)	(N=306)	(N=298)	(N=301)	(N=301)	(N=97)	(N=99)	(N=100)	(N=106)	(N=99)
Local reaction at injection site									
Pain									
77.9%	78.4%	60.1%	66.1%	58.1%	70.1%	80.8%	56.0%	93.4%	69.7%
Swelling									
8.5%	8.8%	6.0%	8.3%	6.6%	8.2%	7.1%	2.0%	15.1%	9.2%
Redness									
7.1%	4.2%	6.4%	6.3%	7.0%	6.2%	6.1%	2.0%	11.3%	7.1%
Systemic events									
Fatigue									
64.3%	60.5%	45.3%	52.5%	49.2%	67.0%	63.6%	38.0%	68.9%	52.0%
Headache									
47.6%	45.1%	26.5%	36.5%	33.6%	49.5%	44.4%	29.0%	46.2%	34.7%
Muscle pain									
33.7%	28.4%	19.8%	23.9%	22.3%	27.8%	32.3%	21.0%	40.6%	23.5%
Chills									
31.6%	26.1%	16.4%	25.6%	13.0%	22.7%	15.2%	13.0%	26.4%	22.4%
Joint pain									
23.5%	15.0%	9.1%	16.6%	11.3%	11.3%	17.2%	12.0%	23.6%	14.3%
Fever (≥38.0°C)									
8.5%	7.2%	3.7%	8.3%	5.0%	9.3%	5.1%	8.0%	11.3%	14.3%
Vomiting									
2.7%	1.6%	1.3%	3.0%	1.7%	3.1%	2.0%	1.0%	1.9%	3.1%
Diarrhea									
8.5%	11.8%	4.4%	8.0%	9.0%	6.2%	13.1%	8.0%	13.2%	7.1%
Use of Antipyretic or pain medication									
38.8%	39.5%	26.8%	34.9%	29.2%	35.1%	30.3%	30.0%	50.9%	38.8%

a. BNT162b2-experienced participants (18 to 55 years of age) who received either BNT162b2 30 µg or BNT162b2 OMI 30 µg as a booster (Dose 4) approximately 3 to 6 months (90 to 180 days) after their last dose (Dose 3).
b. BNT162b2-experienced participants (>55 years of age) who received BNT162b2 30 µg or BNT162b2 OMI 30 µg or BNT162b2 + BNT162b2 OMI 30 µg as a booster dose (Dose 4) approximately 5 to 12 months after their last dose (Dose 3).
c. BNT162b2-experienced participants (≥12 years of age) who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30- or 60-µg as a booster dose (Dose 4) approximately 150 to 365 days after their last dose (Dose 3).

2.5.7. Discussion on clinical safety

To support the inclusion of children aged 5-<12 years to receive a booster dose (dose 4) of the bivalent vaccine Original/BA.4-5 5/5µg, the MAH has submitted 7-day post dose safety data from study C4591044 cohort 2 in which Original/BA.4-5 30µg or 60µg was used, has also been submitted. This included 503 participants ≥12 years of age. Furthermore, the MAH also submitted data from study C4591031 substudies D (18-55 years) and E (>55 years) which included bivalent Original/BA.1 and was evaluated previously in EMEA/H/C/005735/II/0140. Overall, this study showed acceptable reactogenicity for Original/BA.1 in those aged >55, and for a monovalent BA.1 vaccine in those aged 18-55.

None of the studies includes children aged 5-<12 years of age.

Study C4591044 cohort 2 included in total 503 participants divided into three age groups that included about 100 participants each: 12-17 years, 18-55 years and >55 years of age. The participants aged 12-17 years received Original/BA.4-5 30 µg only, whereas the two older age groups received either Original/BA.4-5 30 µg or 60 µg as a fourth dose. All participants had previously received three doses of Comirnaty 30 µg, and a majority received their fourth dose ≥7 to ≤12 months after dose 3.

At this stage, only safety data 7 days after dose 4 has been submitted. No other vaccine than the bivalent Original/BA.4-5 and no placebo groups was included in the study. Therefore, there is no randomised reference group.

Pain at injection site was the most reported local reaction in all study groups. A dose and age dependent pattern were noted, where the highest frequency of all local reactions was observed among the participants 18-55 years of age that received Original/BA.4-5 60 µg and the lowest frequency of local reactions was among the participants aged >55 years of age that received Original/BA.4-5 30 µg.

Among the participants aged 12-17 years of age 70% reported pain at injection site, the corresponding number for the age group 18-55 years was 81%. Most local reactions were mild to moderate at intensity, however, a higher frequency of moderate intensity was noted for pain at injection site in the youngest age group.

Among the systemic events, fatigue (67-69%) and headache (40-46%) occurred at a similar frequency among all participants aged <55 years, and at lower frequency among participants >55 years.

Fever was reported in 9% of the participants aged 12-17 years, and in 5% among the participants aged 18-55 years that received Original/BA.4-5 30µg. The highest frequency of fever (11-14%) was reported among the participants ≥18 years that received the highest dose of the bivalent vaccine.

Most of the events were mild to moderate, it was however noted that a higher frequency of moderate was noted in the youngest age groups for fatigue, headache and muscle pain, where the older age group reported a higher number of mild events instead.

AEs reported within 7 days after dose were overall related to reactogenicity. No severe or serious AEs occurred during that period.

No post-marketing data for the bivalent Original/BA.4-5 vaccine have been submitted.

Data on safety/reactogenicity from Study C4591048 substudy D, which includes 100 children aged 5-<12 years, is awaited early 2023.

Based on these results, overall, a dose- as well as age-depending difference was noted, where the participants aged >55 years tend to have a lower frequency of reactogenicity events and participants receiving a higher dose tend to have a higher frequency of reported events related to reactogenicity. This is in line with what has previously been observed for BNT162b2 vaccines. The reactogenicity profile for Original/BA.4-5 obtained in study C4591044 cohort 2, appears overall to be in line with the reactogenicity profile observed for bivalent Original/BA.1 and Original 30µg as studied in C4591031 substudy D and E in participants aged ≥18 years.

In studies previously evaluated (EMEA/H/C/005735/X/0077) for Original 10µg for children aged 5-<12 years of age, the dose finding study included 10, 20 and 30µg. The dose 10µg was selected and further evaluated in phase 2/3 trials, in which the results supported 10µg to be a suitable dosing with an acceptable reactogenicity profile that did not diverge from the adult population. For the bivalent vaccine intended for use in children aged 5-<12 years of age, the selected dose for the updated Original/BA.4-5 is similar (5+5µg) to Original (10µg). Together with the presented reactogenicity data provided from participants aged ≥12 years who have received Original/BA.4-5 (15/15µg), it is considered unlikely that Original/BA.4-5 (5/5µg) would differ in reactogenicity.

2.5.8. Conclusions on the clinical safety

Overall, the reactogenicity profile in participants >12 years of age who have received Original/BA.4-5 (15/15µg) are in line with what can be anticipated from a vaccine with mostly mild to moderate

reaction. The suggested dose (5/5µg) is similar as for the for children aged 5-<12 years authorized Original 10µg, and it is considered unlikely that reactogenicity would differ. Data on reactogenicity from Study C4591048 substudy D, which includes 100 children aged 5-<12 years, is awaited early 2023.

2.6. Risk Management Plan

2.6.1. Safety concerns

Important Identified Risks	Anaphylaxis
Important Potential Risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

2.6.2. Pharmacovigilance plan

Study (*study short name, and title*) Status (*planned/on-going*)	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
Category 3					
C4591001 *Ongoing*	Global	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine. An imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in frail patients with co-morbidities (C4591001 subset) Long term safety data.	CSR submission upon regulatory request:	Any time
				CSR submission 6 months post Dose 2:	31-May-2021
				Final CSR submission with supplemental follow-up:	31-Dec-2023
C4591007 *Ongoing*	Global	The purpose of the dose-finding/selected-dose study is to rapidly describe the safety, tolerability, immunogenicity, and efficacy of the BNT162b2 RNA-based COVID-19 vaccine candidate against COVID-19 in healthy children.	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long term safety data.	Final CSR submission:	03-Dec-2024
C4591009 *Ongoing*	US	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, among individuals in the general US population and in subcohorts of interest within selected data sources participating in the US Sentinel System.	Myocarditis and pericarditis AESI-based safety events of interest Use in pregnancy Use in immunocompromised patients	Protocol submission:	31-Aug-2021
				Protocol amendment submission:	11-Jul-2022
				Monitoring report 1 submission:	31-Oct-2022
				Monitoring report 2 submission:	31-Oct-2024
				Interim Analysis submission:	31-Oct-2023
				Final CSR submission:	31-Mar-2026
C4591011 *Planned*	US	To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine.	Myocarditis and pericarditis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes,	Interim reports submission:	30-Sep-2022
					31-Dec-2022
				Final CSR submission:	31-Dec-2023

			chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.		
C4591012 *Ongoing*	US	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine including the bivalent Omicron modified vaccine, if feasible.	Myocarditis and pericarditis AESI-based safety events of interest including vaccine associated enhanced disease Use in immunocompromised patients. Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission:	30-Jun-2021 31-Dec-2021 30-Jun-2022 31-Dec-2022
				Final CSR submission	31-Dec-2023
C4591010 *Ongoing*	EU	To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates.	AESI-based safety events of interest Use in pregnancy Long-term safety data.	Final CSR submission	30-Sep-2024
C4591015 *Ongoing*	Global	To assess safety and immunogenicity in pregnant women In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.	Use in pregnancy and while breast feeding.	Final CSR submission:	30-Apr-2023

C4591014 *Ongoing*	US	To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction in all authorized age groups.	Not Applicable.	Final CSR submission:	30-Jun-2023
				Protocol amendment (for bivalent Omicron-modified vaccine) submission:	31-Dec-2022
				Final CSR (for bivalent Omicron-modified vaccine) submission:	30-Jun-2024
WI235284 *Ongoing*	US[a]	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Final CSR submission:	30-Jun-2023
WI255886 *Ongoing*	Ex-EU[a,b]	To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction in individuals 18 years of age and older.	Not Applicable.	Final CSR submission:	30-Jun-2023
				Protocol amendment (for bivalent Omicron-modified vaccine) submission:	31-Dec-2022
				Final CSR (for bivalent Omicron-modified vaccine) submission:	30-Jun-2024
BNT162-01 Cohort 13 *Ongoing*	EU	To assess potentially protective immune responses in immunocompromised adults.	Use in immunocompromised patients.	IA submission:	30-Sep-2021
				Final CSR submission:	31-Oct-2023
C4591024 (former Safety and immunogeni	Global	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years:	Use in immunocompromised patients	Protocol submission:	30-Jun-2021

city in high-risk adults) *Ongoing*		NSCLC, CLL, in hemodialysis for end-stage renal disease).	Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders.	Final CSR submission:	30-Jun-2023
C4591021 (former ACCESS/VAC 4EU) *Ongoing*	EU	Assessment of potential increased risk of adverse events of special interest (AESI) after being vaccinated with COVID-19 mRNA vaccine including bivalent Omicron modified vaccine in all authorized age groups, including individuals less than 12 years of age, if feasible. Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.	Myocarditis and Pericarditis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long term safety data.	Final CSR submission:	30-Sep-2024
C4591038 (former C4591021 substudy) *Planned*	EU	To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine.	Myocarditis and Pericarditis Long term safety data.	Protocol submission:	31-Jan-2022
				Final CSR submission:	30-Sep-2024
C4591022 *Ongoing*	US/CA	To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age.	Use in pregnancy.	Interim reports submission:	31-Jan-2022
					31-Jan-2023
					31-Jan-2024
				Final CSR submission:	31-Dec-2024

C4591036 (former Pediatric Heart Network Study) *Planned*	US/CA	To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis including myocarditis after the bivalent Omicron modified vaccine, if feasible.	Myocarditis/pericarditis Long term safety data.	Protocol submission:	30-Nov-2021
				Final CSR submission:	31-Dec-2029
C4591030 (Co-administration study with seasonal influenza vaccine) *Completed*	Australia, New Zealand	Safety and immunogenicity of COVID-19 mRNA vaccine and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines.	Protocol submission:	17 Aug 2021
				Final CSR submission:	28-
C4591031 Substudy E *Ongoing*	Global	To describe the safety and tolerability profile of BNT162b2 (30 and 60 µg), BNT162b2 OMI (30 and 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants >55 years of age. To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in participants 18 to 55 years of age.	Not applicable[c] Reactogenicity as partial proxy to the general safety profile	Interim reports submission (> 55 y):	31-Aug-2022
				Interim reports submission (18 - to 55 y):	31-Oct-2022
				6M Final CSR submission (>55 y):	31-Jan-2023
				6M Final CSR submission (18- to 55 y):	30-Mar 2023
C4591044 *Ongoing*	US	To describe the safety/tolerability and immune response to BNT162b5 Bivalent and BNT162b2 Bivalents given as a 2nd booster dose to COVID-19-vaccine-experienced participants ≥12 years of age.	Not applicable[c] Reactogenicity as partial proxy to the general safety profile	Protocol Submission:	14-Jun-2022
				Protocol amendment 1 submission:	28-Jul-2022
				Protocol amendment 2 submission:	23-Sep-2022
				Final CSR submission:	30-Sep-2023
C4591048 *Ongoing*	US	To describe the safety/tolerability and immune response to bivalent BNT162b2 given as: SSB, SSC, SSD: 3rd and/or 4th dose to COVID-19-vaccine-experienced participants 6 months to < 12 years of age	Not applicable[c]	Protocol Submission:	23-Sep-2022
				Final CSR submission:	31-May-2025

		SSA: primary bivalent series in COVID-19 vaccine-naïve participants 6 months to <2 years.			

a. Case-control study nested in a prospective surveillance cohort, conducted as a research collaboration.
b. United Kingdom.
c. Vaccine effectiveness

2.6.3. Risk minimisation measures

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Myocarditis and pericarditis	Routine risk minimisation measures: SmPC sections 4.4. and 4.8. Additional risk minimisation measures: DHCP letter and communication plan	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date) C4591009 (31-Mar-2026) C4591011 (31-Dec-2023) C4591012 (31-Dec-2023) C4591021 (former ACCESS/VAC4EU) (30-Sep-2024). C4591038 (former C4591021 substudy) (30-Sep-2024) C4591036 [former Pediatric Heart Network study] (31-Dec-2029).
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about the nature and severity of COVID-19 illness in individuals who have received the COVID-19 mRNA vaccine and is anticipated to provide insight into potential cases of vaccine lack of effect or VAED Additional pharmacovigilance activities: Studies (Final CSR Due Date) C4591001 (31-Dec-2023) C4591007 (03-Dec-2024) C4591009 (31-Mar-2026) C4591011[b] (31-Dec-2023) C4591012[b] (31-Dec-2023) C4591021 (former ACCESS/VAC4EU) (30 Sep-2024)[b].
Use in pregnancy and while breast feeding	Routine risk minimisation measures: SmPC section 4.6; PL section 2. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	No risk minimisation measures.	C4591009 (31-Mar-2026) C4591010[a](30-Sep-2024) C4591011[a] (31-Dec-2023) C4591015 (30-Apr-2023) C4591021 (former ACCESS/VAC4EU)[a] (30-Sep-2024). C4591022a (31-Dec-2024)
Use in immunocompromised patients	Routine risk minimisation measures: SmPC sections 4.4 and 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR or IA Due Date) BNT162-01 Cohort 13 (IA: 30-Sep-2021, CSR: 31-Oct-2023) C4591010[c] (30-Sep-2024) C4591011 (31-Dec-2023) C4591012 (31-Dec-2023) C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)
Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: SmPC section 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date) C4591001 subset (31-Dec-2023) C4591011 (31-Dec-2023) C4591012 (31-Dec-2023) C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date) C4591011 (31-Dec-2023) C4591012 (31-Dec-2023) C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Interaction with other vaccines	Routine risk minimisation measures: SmPC section 4.5. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date) C4591030 (Co-administration study with seasonal influenza vaccine) (28-Feb-2023).
Long term safety data	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date) C4591001 (31-Dec-2023) C4591007 (03-Dec-2024) C4591010 (30-Sep-2024) C4591011 (31-Dec-2023) C4591012 (31-Dec-2023) C4591021 (former ACCESS/VAC4EU) (30-Sep-2024). C4591038 (former C4591021 substudy) (30-Sep-2024) C4591036 (former PHN) (31-Dec-2029)

a. Please note that studies C4591009, C4591010, C4591011, C4591021 (former ACCESS/VAC4EU) and C4591022 address only "Use in pregnancy" and not "Breast feeding".
b. Addresses AESI-based safety events of interest including vaccine associated enhanced disease
c. Addresses AESI-based safety events of interest.

2.6.4. Conclusion

The CHMP considered that the risk management plan version 9.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports 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.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Comirnaty 30 micrograms/dose concentrate for dispersion for injection, EMEA/H/C/005735. The bridging report submitted by the MAH has been found acceptable.

2.8.2. Labelling exemptions

The following exemptions from labelling requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the Questions and Answers on labelling flexibilities for COVID-19 vaccines (EMA/689080/2020 rev.1, from 16 December 2020)5 document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID19 vaccines for EU citizens within the existing legal framework.

Labelling exemptions

Outer and immediate labelling (from start of supply to end March 2023).

The following exemptions are temporarily agreed for the labelling. These exemptions are justified on the necessity to label batches ahead of time.

Outer carton

- Strength: '5/5 micrograms per dose' (initially proposed)', instead of '(5/5 micrograms)/dose' (agreed during evaluation with brackets).
- Common name/INN: common name 'COVID-19 mRNA Vaccine (nucleoside modified)' (initially proposed), instead of common name 'COVID-19 mRNA Vaccine (nucleoside modified)' and INN 'tozinameran/riltozinameran'' (during evaluation).
- Statement of the active substance: "One dose contains 5 micrograms tozinameran and 5 micrograms mRNA encoding Omicron BA.4 and BA.5", instead of "One dose contains 5 micrograms tozinameran and 5 micrograms famtozinameran" (agreed during the assessment)".
- "(After dilution, each vial contains 10 doses of 0.2 mL.)" with text brackets (initially proposed) instead of "After dilution, each vial contains 10 doses of 0.2 mL."; agreed during evaluation (without brackets).
- MA number with 'XXX' placeholder, instead of MA number will be used after approval.

Vial label

- Omission of the Common name/INN due to space limitation.

2.8.3. Quick Response (QR) code

The updates of the QR code/URL to include further references to Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection, as well as the necessary layout changes on the website shall be submitted and assessed via an Article 61.3 notification (post-authorisation).

2.8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, COMIRNATY (tozinameran) is included in the additional monitoring list as a new active substance and new biological.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

After emerging as a human pathogen causing COVID-19, SARS-CoV-2 has continuously evolved and appeared in several variants causing new waves of infection. The strain causing the latest waves of disease has been the Omicron, with several subvariants beginning with BA.1. Currently BA.5 is dominating in the EU.

The sought indication is for booster use:

"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 who have previously received at least a primary vaccination course against COVID-19 (see sections 4.2 and 5.1).

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

3.1.2. Available therapies and unmet medical need

While the efficacy of available vaccines emulating the Wuhan strain against severe disease due to Omicron appears largely retained, efficacy against symptomatic disease is obviously reduced. Moreover, the duration of protection with the original vaccine may be reduced given that the emerging variant is less sensitive than the original target.

Bivalent variant mRNA vaccines containing the original strain as well as BA.1. and BA.4/5 were approved for boosting in the EU in September. SARS-CoV-2 evolution has been rapid, and as stated above the dominating variant at the present time is no longer BA.1 but BA.5.

Currently available therapies have different benefit-risk considerations depending on the stage of illness and disease manifestations. While care for individuals who have COVID-19 has improved with clinical experience, vaccination is the most effective medical countermeasure to decrease risk and

mitigate spread of the SARS-CoV-2 virus during the ongoing pandemic. At this stage, there is no approved COVID-19 vaccine including BA.4-5 for children aged 5-<12 years of age.

3.1.3. Main clinical studies

No clinical studies including efficacy or immunogenicity were submitted in the current application concerning booster dose with Original/Omicron BA.4-5 (5/5) micrograms/dose for the age group 5-<12-year-old children.

Safety data have been submitted from study C4591044 cohort 2 in which 503 participants ≥12 years received either Original/BA.4-5 30µg or 60µg. Furthermore reference is made to study C4591031 Substudy D and E which included bivalent Original/BA.1 and was evaluated previously in EMEA/H/C/005735/II/0140. None of the studies include children aged 5-<12 years of age.

3.2. Favourable effects

It has been demonstrated that boosting with a bivalent Original/BA.1 vaccine confers increased immunogenicity against BA.1 compared to Original alone, as well as non-inferior immunogenicity to the original strain, while having the same total mRNA content. It is assumed that the same would be the case for the Original/BA.4-5 vaccine versus BA.4, BA.5 and the original virus. Data from immunogenicity studies in mice give some support for this notion.

Booster dose of Original Comirnaty 10 µg has been demonstrated to be immunogenic in age group 5-<12 year of old and therefore extrapolation of immunogenicity of a booster dose of Original/Omicron BA.4-5 5/5 µg in this age group can be anticipated.

3.3. Uncertainties and limitations about favourable effects

The size of any increment of immunogenicity against BA.4-5 compared to Comirnaty Original is not known. Moreover, since there is no immune correlate of protection, the extent of increased efficacy given a certain increment in immunogenicity, is also not known. The same pertains to the breadth of the immune response as well as the duration of protection.

The former will be illustrated by immunogenicity data from study C4591044 for age group 12-17 years of age. Immunogenicity data from C4591048 for the age group between 5 – 11 years of age is also expected post-approval.

Observational studies ("real life data") are anticipated to inform on the effectiveness of Original/BA.4-5.

3.4. Unfavourable effects

7-day post-dose safety data from study C4591044 cohort 2 including 503 participants ≥12 years of age to which Original/BA.4-5 30µg or 60µg was administered as a fourth dose, has been presented. Overall, the reactogenicity profile in these participants who received Original/BA.4-5 (15/15µg) are in line with what can be anticipated from a vaccine with mostly mild to moderate reaction. As slightly higher frequency of events related to reactogenicity was noted among the participants ≥18 years of age that received (30+30µg), and a trend to lower frequency of reactogenicity among subject >55 years of age compared with adults aged 18-55 years. This is in line with data presented for the Original vaccine.

3.5. Uncertainties and limitations about unfavourable effects

There are currently no data on the bivalent Original/BA.4-5 variant vaccine in children aged 5-<12 years of age. Data on reactogenicity from Study C4591048 substudy D, which includes 100 children aged 5-<12 years, is awaited early 2023.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

While protection against severe disease remains high, the efficacy against any clinical disease of Comirnaty Original is lower against Omicron strains, compared to what was seen against Wuhan and the Alpha-Delta variants. At this stage, only vaccine based on the Wuhan strain are authorized for children aged 5-<12 years.

There are no data available for Original/BA.4-5 (5/5µg) in participants aged 5-<12 years of age.

It has been demonstrated that boosting with a bivalent Original/BA.1 vaccine confers increased immunogenicity against BA.1 compared to Original alone, as well as non-inferior immunogenicity to the original strain, while having the same total mRNA content. It is assumed that the same would be the case for the Original/BA.4-5 vaccine versus BA.4, BA.5 and the original virus. Data from immunogenicity studies in mice give some support for this notion.

Reactogenicity data from 503 participants ≥12 years of age that have received Original/BA.4-5 15+15 or 30+30 µg have been presented.

In studies previously evaluated (EMEA/H/C/005735/X/0077) for Original 10µg for children aged 5-<12 years of age, the dose finding study included 10, 20 and 30µg. The dose 10µg was selected and further evaluated in phase 2/3 trials, in which the results supported 10µg to be a suitable dosing with an acceptable reactogenicity profile that did not diverge from the adult population. For the bivalent vaccine intended for use in children aged 5-<12 years of age, the selected dose for the updated Original/BA.4-5 is similar (5+5µg) to Original (10µg). Together with the presented reactogenicity data provided from participants aged ≥12 years that have received Original/BA.4-5 (15/15µg), it is considered unlikely that Original/BA.4-5 (5/5µg) would differ in reactogenicity.

Data on reactogenicity from Study C4591048 substudy D, which includes 100 children aged 5-<12 years will receive Original/BA.4-5 (5/5µg) is awaited early 2023. The MAH has committed to providing safety and immunogenicity data from the ongoing C4591048 study in children 5-11 years of age.

Overall, the reactogenicity profile in participants >12 years of age that have received Original/BA.4-5 (15/15µg) are in line with what can be anticipated from a vaccine with mostly mild to moderate reaction. The suggested dose (5+5µg) is similar as for the for children aged 5-<12 years authorized Original 10µg, and it is considered unlikely that reactogenicity would differ.

3.6.2. Balance of benefits and risks

The benefit/risk balance of Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose for the sought indication "active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years who have previously received at least a primary vaccination course against COVID-19" is positive.

3.7. Conclusions

The overall benefit/risk balance of COMIRNATY is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety, the CHMP considers by consensus that the benefit-risk balance of Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose is favourable in the following indication(s):

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 who have previously received at least a primary vaccination course against COVID-19 (see sections 4.2 and 5.1).

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

The CHMP therefore recommends the extension(s) of the marketing authorisation for COMIRNATY subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports 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.

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.