22 June 2023
EMA/355550/2023
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/0176

Note

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

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List of abbreviations

Abbreviation	Definition
AE	adverse event
CDC	Centers for Disease Control and Prevention
CMC	Chemistry Manufacturing and Controls
CO	Clinical Overview
COVID-19	coronavirus disease 2019
DART	Development and Reproductive Toxicology
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EU	European Union
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GMT	geometric mean titer
IM	intramuscular
LNP	lipid nanoparticles
modRNA	nucleoside-modified messenger RNA
mRNA	messenger RNA
n	number of participants
N-binding	SARS-CoV-2 nucleoprotein-binding
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PI	prescribing information
RNA	ribonucleic acid
RSV	respiratory syncytial virus
SARS	severe acute respiratory syndrome
SAE	serious adverse event
SARS-CoV-2	SARS coronavirus-2
UK	United Kingdom
US	United States
VE	vaccine efficacy
VOC	variant of concern
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WT	wild-type

1. Background information on the procedure

1.1. Submission of the dossier

BioNTech Manufacturing GmbH submitted on 03 March 2023 an extension of the marketing authorisation.

Extension application to add a new strength of 1.5/1.5 micrograms/dose for the Comirnaty Original/Omicron BA.4-5 concentrate for dispersion for injection for infants and children between 6 months to 4 years of age.

The MAH applied for an addition of a new strength 1.5/1.5 micrograms/dose.

The MAH applied for the following indication for Comirnaty 1.5/1.5 micrograms/dose:

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.

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 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 appointed by the CHMP was:

Rapporteur: Filip Josephson

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Menno van der Elst

The application was received by the EMA on	03 March 2023
The procedure started on	25 March 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 May 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 June 2023
ETF discussions took place on	13 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	15 June 2023
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	22 June 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human-to-human transmission.

2.1.2. Clinical presentation

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.

Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhoea, headache, weakness, and rhinorrhoea. Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.

2.1.3. 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.

2.2. About the product

Given the genetic and resulting antigenic differences in currently circulating Omicron sublineages of SARS-CoV-2 (eg, BQ.1, BQ.1.1, BA.5, XBB.1, XBB.1.5) compared to the original strain, the MAH has added the bivalent variant-adapted vaccine to ensure adequate protection in children <5 years of age, as is currently authorized for booster doses in individuals ≥5 years of age. The protection provided by the original type-based mRNA vaccines against Omicron-related infection appears to be lower and shorter-lived compared to that seen for prior variants. Vaccine effectiveness against severe disease associated with novel Omicron sublineages has waned even for severe disease among the general population with a booster dose.

The bivalent COMIRNATY Original/Omicron BA.1 vaccine and the bivalent COMIRNATY Original/Omicron BA.4/BA.5 vaccine were approved in the EU for use in individuals ≥12 years of age who have received at least primary vaccination against COVID-19 on 01 September 2022 and 12 September 2022, respectively. On 10 November 2022, the 10 µg dose of the bivalent COMIRNATY Original/Omicron BA.4/BA.5 vaccine was approved for use in individuals 5 through 11 years of age who have received at least primary vaccination against COVID-19. The immunogenicity assessment of Original/Omi BA.4/BA.5 was based on extrapolation of immunogenicity data from studies with Comirnaty Original and Original/Omi BA.1 and explorative non-clinical immunogenicity data for the Original/Omi BA.4/BA.5.

2.3. Type of Application and aspects on development

The authorization of a 3-dose primary series of BNT162b2 3 µg in individuals 6 months to <5 years of age is based on clinical safety and immunogenicity data from approximately 4500 participants (including approximately 3000 participants who received BNT162b2 and 1500 who received placebo) 6 months to <5 years of age with 1.3-to-1.4-month median duration of blinded follow-up in Study C4591007. Effectiveness of the 3-µg dose in the 6 months to <5 years of age group was inferred based on the successful protocol-specified immunobridging analysis, which compared SARS-CoV-2 neutralizing antibody responses in this age group in Study C4591007 to a group of young adult participants 16 to 25 years of age in the C4591001 efficacy study. Protocol-specified efficacy analyses demonstrated >70% VE in this age group from at least 7 days post-Dose 3 to the data cutoff date.

Pfizer/BioNTech requested authorization of the 3 µg formulation of the Comirnaty Original/Omicron BA.4-5 Vaccine as a 3-dose primary series and booster (fourth dose) for use in infants and children 6 months to <5 years of age based upon:

- Immunogenicity and safety data for a subset of participants ≥6 months to <5 years of age in Group 2 of Substudy B of Study C4591048 following administration of BNT162b2 Bivalent (Original/OMI BA.4/BA.5) at 3 µg as a booster (fourth dose).
- Extrapolation of immunogenicity and safety data for participants ≥5 years to <12 years of age in Group 2 of Substudy D of Study C4591048 following administration of BNT162b2 Bivalent (Original/OMI BA.4/BA.5) at 10 µg as a booster (fourth dose).
- Extrapolation of immunogenicity and safety data from participants in Cohort 2 (≥12 years of age) and Cohort 3 (≥18 years of age) of Study C4591044 following administration of BNT162b2 Bivalent (Original/OMI BA.4/BA.5) at 30 or 60 µg as a booster (fourth dose).
- BNT162b2 Bivalent (original/OMI BA.4/BA.5) 3 µg specific CMC package.

Thus, no data are available for primary vaccination with the bivalent BNT162b2 (Original/Omicron BA.4-5).

2.4. Quality aspects

2.4.1. 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 several approved formulations of Comirnaty vaccine:

- PBS/Sucrose finished product, *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, *Comirnaty, 30 micrograms/dose, dispersion for injection*, approved 3 November 2021 (EMEA/H/C/005735/X/0044)
- Tris/Sucrose finished product, *Comirnaty, 10 micrograms/dose, concentrate for dispersion for injection,* approved 26 November 2021 (EMEA/H/C/005735/X/0077)
- Tris/Sucrose finished product, *Comirnaty Original/Omicron BA.1, (15/15 micrograms)/dose, dispersion for injection*, approved 1 September 2022 (EMEA/H/C/005735/II/0140)
- 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)
- Tris/Sucrose finished product, *Comirnaty, 3 micrograms/dose, concentrate for dispersion for injection,* approved 20 October 2022 (EMEA/H/C/005735/X/0138)
- Tris/Sucrose finished product, *Comirnaty Original/Omicron BA.4-5, (5/5 micrograms)/dose, concentrate for dispersion for injection*, approved 10 November 2022 (EMEA/H/C/005735/X/0147)
- Tris/Sucrose finished product, *Comirnaty Original/Omicron BA.4-5, (5/5 micrograms)/dose, dispersion for injection*, under review, outcome June 2023 (EMEA/H/C/005735/X/180)

To assist in the public health crisis, a new Pediatric 3 µg BNT162b2 Bivalent [Original and Omicron (BA.4/BA.5) variant] finished product (herein referred to as Bivalent or 3 µg dose), consisting of the Original and Omicron (BA.4/BA.5) active substance strains (also referred to as active substance constructs), is being introduced.

The purpose of this submission is to provide details on the Bivalent finished product 3 µg RNA dose presentation, which is filled at 0.4 mL per vial. The 3 µg RNA presentation requires dilution with 2.2 mL 0.9% sodium chloride prior to administration and once diluted provides 10 doses, each containing a 3 µg RNA dose in 0.2 mL injection volume.

The Bivalent vaccine is manufactured using the two active substance RNA constructs in an approximately 1:1 ratio The Bivalent finished product is formulated at 0.1 mg/mL RNA in Tris buffer and sucrose. The platform manufacturing processes from the Original Tris-Sucrose and Bivalent finished product are used for the manufacture of 3 µg dose. Substantial supportive process and characterisation information is available for both the Original Tris-Sucrose and Bivalent finished products. From an active substance perspective, there are no changes to the manufacture, characterisation, control, container closure, or stability required on the basis of this change. Similarly, from a finished product perspective, there are no changes to finished product control of excipients or container closure on the basis of this change. The 3 µg dose finished product is identical to the 10 and 30 µg dose finished products, differing only in fill volume and dose specific requirements for dilution prior to administration.

2.4.2. Active Substance

The active substances tozinameran and famtozinameran are already approved for the original Comirnaty vaccine formulations (EU/1/20/1528/001-014). No changes to the information are proposed except for a minor and acceptable update in section 3.2.S.4.5.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and Pharmaceutical Development

The BNT162b2 Bivalent (Original and Omicron (BA.4/BA.5) Variant) finished product, is supplied as a preservative-free, sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer for intramuscular administration.

The Bivalent finished product is formulated at 0.1 mg/mL RNA in Tris bufferand sucrose,and contains an approximately 1:1 ratio of the BNT162b2 Original and Omicron BA.4/BA.5 RNA constructs. There are three dosages of the Bivalent finished product – 30, 10, and 3 µg RNA per dose. The doses differ only in the fill volume and requirement for dilution prior to administration:

- The Bivalent finished product 30 µg RNA dose is provided in either the multidose (MDV) presentation filled at 2.25 mL fill volume and is administered without dilution, providing 6 doses, each a 30 µg RNA dose in 0.3 mL injection volume or the 30 µg RNA dosage is provided in a single dose (SDV) presentation filled at 0.48 mL fill volume and administered without dilution, providing one 30 µg RNA dose in 0.3 mL injection volume. Each construct, BNT162b2 Original and Omicron BA.4/BA.5 is present in approximately equal quantities, i.e. 15 µg RNA each, totalling 30 µg RNA per dose.

- The Bivalent finished product 10 µg RNA dose is filled at 1.3 mL fill volume and 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 construct, BNT162b2 Original and Omicron BA.4/BA.5, is present in approximately equal quantities, i.e. 5 µg RNA each, totalling 10 µg RNA per dose.
- The Bivalent finished product 3 µg RNA dose is filled at 0.4 mL fill volume and requires dilution with 2.2 mL 0.9% sodium chloride prior to administration, providing 10 doses, each a 3 µg RNA dose in 0.2 mL injection volume. Each construct, BNT162b2 Original and Omicron BA.4/BA.5, is present in approximately equal quantities, i.e. 1.5 µg RNA each, totalling 3 µg RNA per dose.

The section on description and composition of the finished product has been updated to include the 3 µg dose presentation of the bivalent vaccine compared to the already approved procedures EMEA/H/C/005735/X/0077 (10 µg dose presentation), EMEA/H/C/005735/X/0138 (3 µg dose presentation) EMEA/H/C/005735/X/0147 (10 µg, bivalent dose presentation including the original and omicron BA.4/BA.5 strains) and EMEA/H/C/005735/II/0143 (30 µg, bivalent dose presentation including the original and omicron BA.4/BA.5 strains).

The composition of the bivalent finished product 3 µg RNA dose, including quality standard, function, concentration and amount per dose has been provided.

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 QTPP has been updated for the bivalent vaccine to include the bivalent 3 µg/dose 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 for the claimed shelf-life.

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 sections on components of the finished product and manufacturing process development and characterization have been updated to include the bivalent 3 µg/dose presentation.

Comparability has previously been convincingly demonstrated for a number of comparisons of Comirnaty finished product, such as between clinical and commercial scale original finished product, between various manufacturing sites, between the PBS/Sucrose finished product and Tris/Sucrose finished product, between the various dosage presentations (30 µg, 10 µg and 3 µg) as well as between the monovalent and bivalent vaccine finished product. Comparability has been demonstrated via comprehensive studies including both release testing and extended characterisation testing. Due to the application of the same formulation, manufacturing process, and the use of the same manufacturing sites as the original and authorised finished product, extensive prior experience is leveraged for the bivalent 3 µg/dose vaccine finished product and comparability previously convincingly proven and concluded.

For the bivalent 3 µg/dose presentation of finished product, batch analysis data are provided for a large-scale confirmatory batch with a fill volume of 0.4 mL.

In conclusion, the information provided in the sections on Description and composition of the finished product and Pharmaceutical development is found sufficient and acceptable.

2.4.3.2. Manufacture of the product and process controls

The bivalent BA.4-5 vaccine (1.5/1.5 micrograms)/dose is manufactured at manufacturing sites, and using the same platform process, as currently approved Comirnaty vaccines (Tris/Sucrose formulation) (EU/1/20/1528/002-014). The GMP compliance of these sites has been previously confirmed.

The manufacturing process consists of four major manufacturing steps – LNP fabrication, bulk drug 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) and the bivalent BA.4 5 vaccine (5/5 micrograms)/dose (EMEA/H/C/005735/X/147) except for a different 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 (1.5/1.5 micrograms)/dose. This is found acceptable since this line extension is based on the currently approved bivalent vaccines (Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose and (5/5 micrograms)/dose as well as the monovalent Comirnaty 3 micrograms/dos.

2.4.3.3. Product specification, analytical procedures, batch analysis

The finished product specifications for the bivalent vaccine finished product 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 specifications for the bivalent 3 µg/dose vaccine finished product includes a comprehensive set of relevant tests along with corresponding acceptance criteria. The acceptance criteria for release and stability testing for the bivalent 3 µg/dose vaccine finished product are the same as those for the already approved bivalent 10 µg/dose and bivalent 30 µg/dose vaccine finished products for all quality attributes tested, except for vial content (volume) which has different acceptance criteria.

The proposed acceptance criteria for vial content (volume) for the bivalent 3 µg/dose vaccine finished product is identical to the original 3 µg/dose monovalent Tris/sucrose vaccine finished product. The vial content (volume) for Tris/Sucrose finished product was determined to ensure that each 0.4 mL filled vial can deliver up to ten 3 µg doses of 0.2 mL each, following the addition of 2.2 mL 0.9% sodium chloride. The provided justification for vial content (volume) of 0.4 fill volume is found acceptable.

Since the acceptance criteria for the bivalent 3 µg/dose vaccine finished product are based on the currently approved bivalent as well as original Tris/Sucrose vaccine finished products for the majority of test attributes, these acceptance criteria for test attributes are considered as clinically qualified to ensure quality, efficacy and safety.

Batch data has been provided for a commercial scale confirmatory batch filled at 0.4 mL. The batch was manufactured at the commercial site for the bivalent vaccine finished product (30, 10 and 3 µg RNA/dose) at Pfizer, Puurs, BE. All results met the acceptance criteria at the time of release. In addition, stability studies have been initiated and are ongoing for the commercial scale batch.

2.4.3.4. Stability of the product

Batch release data are provided for one commercial scale batch of the bivalent 3 µg/dose vaccine finished product and this batch has been placed on stability study at both long-term storage conditions (-90 to -60°C) and accelerated storage conditions (5 ± 3 °C).

The claimed 18 months shelf-life is identical to the already approved shelf-life for the original vaccine finished product (Tris/Sucrose formulation) and is based on the results provided in several recently approved line extensions EMEA/H/C/005735/X/0044 (30 µg/dose/2.25 mL fill volume), EMEA/H/C/005735/X/0077 (10 µg/dose/1.3 mL fill volume), EMEA/H/C/005735/X/0138 (3 µg/dose/0.4 mL fill volume), EMEA/H/C/005735/II/0143 (bivalent 30 µg/dose/2.25 mL fill volume), EMEA/H/C/005735/X/0147 (bivalent 10 µg/dose/2.25 mL fill volume) as well as from stability results for the bivalent 3 µg/dose vaccine finished product provided in this specific line extension EMEA/H/C/005735/X/0176.

This approach to extrapolate the shelf-life from the already authorised vaccine finished products, including both monovalent and bivalent finished products, is found acceptable since comparability has been convincingly demonstrated for a number of various comparisons of Comirnaty finished product such as between clinical and commercial scale finished product, between various manufacturing sites, between the PBS/Sucrose and Tris/Sucrose finished product, between the various dosage presentations (30 µg, 10 µg and 3 µg) as well as between the monovalent and bivalent vaccine finished product. Comparability has been demonstrated via comprehensive studies including both release testing and extended characterisation testing. Due to the application of the same formulation, manufacturing process, and the use of the same manufacturing sites as the original and authorized finished product, extensive prior experience is leveraged for the bivalent 3 µg/dose vaccine finished product and comparability previously convincingly proven and concluded.

Therefore, it was concluded that the proposed shelf-life for the bivalent 3 µg/dose vaccine finished product of 18 months when stored at the recommended storage temperature of -90 to -60°C, including a short-term storage at 2-8 °C for up to 10 weeks (within the 18 months shelf-life), as defined in SmPC Section 6.3, is acceptable.

2.4.3.5. Post approval change management protocol(s)

Not applicable.

2.4.3.6. Adventitious agents

The active substances (tozinameran and famtozinameran) are identical to that used for the currently approved Comirnaty vaccine formulations (EU/1/20/1528/001-014). 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.

2.4.3.7. GMO

Not applicable.

2.4.4. 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.

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.

2.4.5. Conclusions on chemical, pharmaceutical and biological aspects

This line extension application to register Comirnaty Original/Omicron BA.4-5, (1.5/1.5 micrograms)/dose, concentrate for dispersion for injection is recommended for approval from a quality point of view.

2.5. Non-clinical aspects

2.5.1. Introduction

New data for this application is limited to studies on the immune response in mice after a primary series with variant vaccines, including the bivalent Omicron BA4/BA5 vaccine.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The monovalent or bivalent Omicron BA.4/BA.5 variant-modified vaccines were tested as a two dose primary series in naïve Balb/c mice and as a 3rd dose booster in BNT162b2-experienced Balb/c mice. Omicron BA.4 and BA.5 sublineages contain the same spike sequence, therefore the vaccine is described as "BA.4/BA.5".

Five groups of 10 female Balb/c mice were immunized, bled and euthanized after either receiving immunizations either twice, at 0 and 21 days, in the primary series; or one month after the primary series completion, as a third dose booster. Blood was collected at baseline and at 7 days and 28 days after last immunization. At 28 days after last immunization, spleen and lymph nodes were also harvested to analyze the antibody response by a pseudovirus neutralization assay and B-cell and T-cell responses by flow cytometry.

Naïve mice were immunized with a two-dose primary series of monovalent OMI BA.4/BA.5 vaccine, which elicited high neutralizing titers against Omicron sub-lineages BA.2, BA.2.12.1, and BA.4/BA.5 after two

doses, but reduced neutralization against the Wuhan pseudovirus and the Omicron BA.1 sub-lineage. The bivalent Omicron BA.4/BA.5 vaccine (combination of BNT162b2 and BNT162b2 Omicron BA.4/BA.5) elicited a greater breadth of neutralizing antibody responses against all variants and sub-lineages tested.

Immunization of BNT162b2-experienced Balb/c mice with either the monovalent or bivalent BA.4/BA.5 variant-modified vaccine as a third dose booster, one month after completion of the primary series, increased neutralizing antibody responses against the Wuhan reference, the Delta variant and Omicron BA.1, BA.2, BA.2.12.1 and BA.4/BA.5 sub-lineages. In the monovalent group, Wuhan, Omicron BA.1, BA.2 and BA.4/BA.5 neutralizing titers increased by 2, 2, 17, and 45-fold, respectively, at 7 days post booster compared to 1 month post BNT162b2 Dose 2. At 1 month post-third dose boost, the difference, as compared to 1 month post BNT162b2 Dose 2, was 4, 7, 36, and 94-fold for Wuhan, Omicron BA.1, BA.2 and BA.4/BA.5, respectively.

In the bivalent group, Wuhan, Omicron BA.1, BA.2, and BA.4/BA.5 neutralizing titers increased by 3, 3, 11, and 22-fold, respectively, 7 days post booster compared to 1 month post BNT162b2 Dose 2 and 3, 6, 17, and 66-fold, respectively, 1 month post booster compared to 1 month post BNT162b2 Dose 2. A broad response against Omicron sub-lineages was achieved with both monovalent (BNT162b2 BA.4/BA.5) and bivalent (BNT162b2 + BNT162b2 BA.4/BA.5) formulations. The monovalent BA.4/BA.5 formulation elicited slightly higher Omicron-specific neutralizing titers compared to the bivalent BA.4/BA.5 formulation.

In BNT162b2-experienced mice, both monovalent and bivalent vaccines administered as a third dose booster elicited a high frequency of total spike-specific B cells against any variant or sublineage with the greatest proportion of the response to Omicron BA.4-antigen. Slightly more cross-reactive B cells were observed with the bivalent BNT162b2+Omicron BA.4/BA.5 vaccine compared to the monovalent Omicron BA.4/BA.5 vaccine. Both monovalent Omicron BA.4/BA.5 and bivalent BNT162b2+Omicron BA.4/BA.5 vaccines induced predominantly Omicron BA.4 strain-specific Spike+ B cells compared to a low frequency of WT or Omicron BA.1 Spike+ B cells.

The magnitude of spike-specific T-cell responses induced by both monovalent and bivalent vaccines was similar. Notably, the magnitude of the T-cell response did not change based on the peptide pool (WT vs Omicron BA.4/BA.5), confirming that the variant- and sub-lineage specific mutations have minimal impact on the polyclonal T-cell response.

Overall, two doses of the monovalent BA.4/BA.5 variant-modified vaccine elicited strong neutralizing antibody responses against Omicron BA.2, BA.2.12.1, and BA.4/BA.5 sub-lineages but reduced neutralizing activity against the Wuhan and BA.1. The bivalent formulation induced a broader immune response against all strains tested. In BNT162b2 experienced mice, BA.4/BA.5 variant-modified vaccines induced robust and broad neutralizing antibody responses against the Wuhan reference and Omicron BA.1, BA.2, BA.2.12, and BA.4/BA.5 sub-lineages as well as a strong spike-specific B-cell and T-cell response when administered as a third dose booster.

2.5.3. Pharmacokinetics

There are no new pharmacokinetics studies for this application. The pharmacokinetics program supporting the original MAA for BNT162b2 is fully supporting the current extension application.

2.5.4. Toxicology

There are no new toxicology studies for this application. The toxicology program supporting the original MAA for BNT162b2 is fully supporting the current extension application.

2.5.5. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100 Corr 2), due to their nature, vaccines and lipids are unlikely to result in a significant risk to the environment. Therefore, an environmental risk assessment is not provided in this Application.

2.5.6. Discussion on non-clinical aspects

To support the use of the bivalent Original/Omicron BA4/BA5 variant vaccine, the MAH has provided data from studies in mice. Compared to the original vaccine, the bivalent Omicron BA.4/BA.5 vaccine (combination of BNT162b2 and BNT162b2 Omicron BA.4/BA.5) elicited a greater breadth of neutralizing antibody responses against all variants and sub-lineages tested.

The magnitude and specificity of the T-cell response was similar with monovalent and bivalent vaccines.

Since the selection of B-cell repertoire activated by the vaccine is likely to be similar between mice and humans, these data are considered supportive for the use of the bivalent Original/Omicron BA4/BA5 vaccine for a primary vaccination.

2.5.7. Conclusion on the non-clinical aspects

The data from studies in mice with the Original/Omicron BA4/BA5 bivalent vaccine are considered supportive for the use of this vaccine for primary vaccination.

2.6. Clinical aspects

2.6.1. Introduction

- **Tabular overview of clinical studies**

Protocol No. Phase (Country)
C4591048 Substudy B Group 2 Safety and Immunogenicity Phase 3 (United States)
C4591048 Substudy D Group 2 Safety and Immunogenicity Phase 3 (United States)

C4591044 Cohort 2 and Combined Cohort 2 (Groups 2& 4) +Cohort 3 (Groups 1& 2) Interim CSR Phase 2/3 (United States)

2.6.2. Clinical efficacy

2.6.2.1. Dose response studies

No data was submitted for dose-finding for Original/Omicron BA. 4-5 1.5/1.5 micrograms.

2.6.2.2. Main study

Overview of the master protocol of C4591048 investigating Comirnaty Original/Omicron BA4-5 in children. The results from substudy B are pivotal and from the substudy D are supportive for the current application.

High-Level Overview of Substudies in Master Protocol for Bivalent BNT162b2

Phase	Group	Dose Level	Number of Doses Administered Prior to Enrollment	Dosing Schedule	Number of Doses to Be Administered During the Study	Approximate Number of Participants
Substudy A: Primary 3-Dose Series + Fourth-Dose Evaluation: Participants ≥6 Months to <4 Years 3 Months of Age						
Phase 1 (age group 1 and age group 2)		3 µg	0	0, 3, and 11 weeks and 6 months after Dose 3	4	60
		6 µg				60
		10 µg				60
Phase 2/3		TBD	0	0, 3, and 11 weeks and 6 months after Dose 3	4	750
		TBD		0, 8, and 16 weeks and 6 months after Dose 3		750
Substudy B: Third- and/or Fourth-Dose Evaluation: Participants ≥6 Months to <4 Years 6 Months of Age (Group 1), Participants ≥6 Months to <5 Years of Age (Groups 2 and 3)						
Phase 3	Group 1	3 µg	2		2	200
	Group 2		3		1	300
	Group 3 (C4591007 rollover)		3		1	3600
Substudy C: Fourth-Dose Evaluation: Participants ≥6 Months to <5 Years of Age						
Phase 1 (age group 1 and age group 2)		6 µg	3		1	60
		10 µg				60
Phase 2/3		TBD			1	400
Substudy D: Third- or Fourth-Dose Evaluation: Participants ≥5 to <12 Years of Age						
Phase 3	Group 1	10 µg	2		1	100
	Group 2		3			100
	Group 3 (C4591007 Phase 1 rollover)		3			50

Table. Overview of C4591048 substudy B investigating Comirnaty Original/Omicron BA4-5 (1.5/1.5 µg) in children 6m-<5yoa

Protocol No. Phase (Country)	Study Design and Objective(s)[a]	Vaccine Groups	No. of Participants
C4591048 Substudy B Group 2 Safety Ad Hoc Report Phase 3 (United States)	**Primary Objectives: Primary Safety (Safety Population):** To describe the safety and tolerability profiles of prophylactic bivalent BNT162b2 given as a third and/or fourth dose in participants ≥6 months to <5 years of age.	**Subset of Substudy B Group 2 (4th dose)** BNT162b2 Bivalent (WT/OMI BA.4-5) 3 µg	BNT162b2 Bivalent (WT/OMI BA.4-5) 3 µg ≥6 Months to <2 Years: N=24 ≥2 Years to <5 Years: N=36

C4591048 Substudy B Group 2 Immunogenicity Ad Hoc Report Phase 3 (United States)	**Secondary Objective: Secondary Immunogenicity (Evaluable Immunogenicity Population):** To describe the immune response elicited by bivalent BNT162b2 given as the third and/or fourth dose in participants ⩾6 months <5 years of age.	**Subset of Substudy B (4th Dose) Group 2** BNT162b2 Bivalent (WT/OMI BA.4-.5) 3 µg **Study C4591007 Subset of Participants** Original BNT162b2 3 µg (3rd dose)	BNT162b2 Bivalent (WT/OMI BA.4-5) 3 µg ≥6 Months to <2 Years: N=23 ≥2 Years to <5 Years: N=35 Original BNT162b2 3 µg ≥6 Months to <2 Years: N=23 ≥2 Years to <5 Years: N=31

2.6.2.2.1. Study C4591048 Substudy B

Title: A Master Phase 1/2/3 Protocol to Investigate the Safety, Tolerability, and Immunogenicity of Bivalent BNT162b2 RNA-Based Vaccine Candidate in Healthy Children

This study includes evaluation of the safety, tolerability, and immunogenicity of third and fourth dose with the bivalent BNT162b2 (Original/Omi BA.4/BA.5) vaccine in individuals ≥6 months to <4 years and 6 months (Group 1) and fourth dose with the bivalent BNT162b2 (Original/Omi BA.4/BA.5) vaccine in ≥6 months to <5 years of age (Group 2 and Group 3 [safety only]).

This report presents 1-month post dose descriptive immunogenicity data, as of the data cut-off date of 25 November 2022, for a subset of 60 participants in Group 2 of C4591048 Substudy B (the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively) who received a fourth dose with the bivalent BNT162b2 (Original/Omi BA.4/BA.5) at the 3 µg dose level after receiving 3 prior doses of BNT162b2 at 3 µg.

Results include also data, as of the data cut-off date of 07 August 2022, from a comparator subset of 60 participants ≥6 months to <5 years of age (24 and 36 participants ≥6 months to <2 years of age and ≥2 years to <5 years of age, respectively) in Study C4591007 who received 3 doses of BNT162b2 at 3 µg.

Table. Schema for C4591048 Substudy B, Group 2

Group 2: 3 Prior Doses of BNT162b2 3 µg 60 to 240 Days Prior to Enrollment

	Visit Number	B201	B202	B203
	Visit Description	Fourth Dose Vaccination Visit	1-Month Follow-Up Visit After Fourth Dose	6-Month Follow-Up Visit After Fourth Dose
Participants having received **3 prior doses** of BNT162b2 3 µg 60 to 240 days prior to enrollment		Bivalent BNT162b2 3 µg		
	Nasal swab	X		
	Blood draw for immunogenicity	5 mL	5 mL	

Methods

Approximately 300 participants in Group 2, ≥6 months to <5 years of age, who have received 3 prior doses of BNT162b2 3 µg, with their last dose 60 to 240 days prior to enrolment, will receive 1 dose (fourth) of bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg.

Enrolment of Group 2 will be stratified by age, such that approximately 30% of participants will be ≥6 months to <2 years of age and approximately 70% of participants will be ≥2 years to <5 years of age.

- **Study Participants**

Included are male or female participants who are ≥6 months to <5 years of age at the time of enrolment, and who have received 3 prior doses of BNT162b2 3 µg, with the last dose 60 to 240 days before enrolment.

Excluded are subjects, who have

1. Receipt of medications intended to prevent COVID-19.

2. Previous or current diagnosis of MIS-C.

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

5. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to systemic lupus erythematosus. Note: Stable type 1 diabetes and hypothyroidism are permitted.

6. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

7. Other medical or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

8. Prior receipt of any COVID-19 vaccine other than BNT162b2.

9. Receipt of systemic treatment with known immunosuppressant medication (including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease) or radiotherapy, within 60 days before enrollment through the conclusion of the study.

10. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies (except palivizumab), from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19 from 90 days before study intervention administration, or planned receipt throughout the study.

11. Receipt of other study intervention within 28 days prior to study entry through and including 28 days after the dose of study intervention, with the exception of non-Pfizer interventional studies

12. Participants who are direct descendants (child or grandchild) of investigational site staff members or Pfizer/BioNTech and Pfizer/BioNTech delegate employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

- **Treatments**

Bivalent BNT162b2 (Original/Omi BA.4_5) at 3 µg (1.5/1.5 µg of each) (C4591048 Substudy B) or Original 3 µg (Study C4591007).

- **Objectives**

Secondary Immunogenicity Objectives, Estimands and Endpoints for C4591048 Substudy B, Group 2

• To describe the immune response elicited by bivalent BNT162b2 given as the third and/or fourth dose in participants ≥6 months <5 years of age.	In participants complying with the key protocol criteria (evaluable participants), for each strain-specific neutralizing titer: • GMTs at each time point • GMFR from before the first study vaccination to each subsequent time point • Percentages of participants with seroresponse[a] at each time point following vaccination	• SARS-CoV-2 Omicron BA.4/BA.5–neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers

- **Outcomes/endpoints**

Secondary immunogenicity:

- SARS-CoV-2 Omicron BA4-5 and Reference strain neutralizing titers (GMT)

- **Sample size**

Approximately 300 participants in Group 2, ≥6 months to <5 years of age, who have received 3 prior doses of BNT162b2 at 3 µg, with their last dose 60 to 240 days prior to enrolment, will receive 1 dose (fourth) of the bivalent BNT162b2 (Original/Omi BA.4/BA.5) at 3 µg.

For the final immunogenicity assessment, a subset of approximately 240 participants will be selected from 300 participants in Group 2 who received 3 prior doses of BNT162b2 3 µg and a fourth dose of bivalent BNT162b2, and approximately 240 participants will be selected from participants receiving 3 doses of BNT162b2 3 µg from the C4591007 study. Assuming a 25% non-evaluable rate, approximately 180 evaluable participants in each arm will contribute to the immunogenicity evaluation. Each hypothesis test will be performed at a 1-sided alpha level of 0.025 as described in Statistical Methods.

In current analysis, the immunogenicity of bivalent vaccine in 60 subjects 6m-5yoa is descriptive and no hypothesis testing will be performed.

- **Randomisation and blinding (masking)**

Substudy B is an open-label study to evaluate the safety, tolerability, and immunogenicity of a third or fourth dose with the bivalent BNT162b2 (Original/Omi BA.4/BA.5) at 3 µg.

Enrolment of Group 2 will be stratified by age, such that approximately 30% of participants will be ≥6 months to <2 years of age and approximately 70% of participants will be ≥2 years to <5 years of age.

- **Statistical methods**

Descriptive immunogenicity analyses were performed to characterize Omicron BA.4/BA.5 and reference strain neutralization responses following a fourth dose with the bivalent BNT162b2 (Original/Omi BA.4/BA.5) or 3 doses of BNT162b2 each at 3 µg. The SARS-CoV-2 neutralization assay was used to determine Omicron BA.4/BA.5- and reference strain-specific neutralizing titers.

GMTs and GMFRs with 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and fold rises, respectively, and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Seroresponse was defined as achieving a ≥4-fold rise from baseline (before the first study vaccination [fourth dose]) for participants. If the baseline measurement was below the LLOQ, the postvaccination measure of ≥4 × LLOQ was considered seroresponse. The exact 2-sided 95% CIs for percentages of participants with seroresponse was calculated using the Clopper-Pearson method.

Analysis Sets

Population	Description
Evaluable immunogenicity (third dose)	All eligible participants in Group 1 who receive the first study intervention as the third dose to which they are assigned, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window after the third dose, and have no other important protocol deviations as determined by the clinician.
Evaluable immunogenicity (fourth dose)	All eligible participants who receive 2 doses of study intervention as the third and fourth dose (Group 1) or receive the study intervention as the fourth dose (Group 2) to which they are assigned, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window after fourth dose, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.

Results

Available immunogenicity data are summarized below for the subset of 60 participants in Group 2 of Substudy B (as of the cut-off date of 25 November 2022) and a comparator subset of 60 participants from Study C4591007 (as of the cut-off date of 07 August 2022).

- **Participant flow**

Immunogenicity Populations – C4591048 Subset of Substudy B Group 2 and Study C4591007 Phase 2/3 Participants – ≥6 Months to <5 Years of Age

	Vaccine Group (as Assigned/Randomized)					
	C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg			C4591007 BNT162b2 3 µg		
	≥6 Months to <2 Years n[a] (%)	≥2 to <5 Years n[a] (%)	≥6 Months to <5 Years n[a] (%)	≥6 Months to <2 Years n[a] (%)	≥2 to <5 Years n[a] (%)	≥6 Months to <5 Years n[a] (%)
Assigned/Randomized[b]	24	36	60	24	36	60
Dose 4 (C4591048)/Dose 3 (C4591007) all-available immunogenicity population	23 (95.8)	35 (97.2)	58 (96.7)	24 (100.0)	36 (100.0)	60 (100.0)
Excluded from Dose 4 (C4591048)/Dose 3 (C4591007) all-available immunogenicity population	1 (4.2)	1 (2.8)	2 (3.3)	0	0	0
Reason for exclusion						
Did not have at least 1 valid and determinate immunogenicity result after Dose 4 (C4591048)/Dose 3 (C4591007)	1 (4.2)	1 (2.8)	2 (3.3)	0	0	0
Dose 4 (C4591048)/Dose 3 (C4591007) evaluable immunogenicity population	23 (95.8)	35 (97.2)	58 (96.7)	23 (95.8)	31 (86.1)	54 (90.0)
Participants without evidence of infection up to 1 month after Dose 4 (C4591048)/Dose 3 (C4591007)[c]	12 (50.0)	26 (72.2)	38 (63.3)	13 (54.2)	21 (58.3)	34 (56.7)
Excluded from Dose 4 (C4591048)/Dose 3 (C4591007) evaluable immunogenicity population	1 (4.2)	1 (2.8)	2 (3.3)	1 (4.2)	5 (13.9)	6 (10.0)
Reason for exclusion[d]						
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 4 (C4591048)/Dose 3 (C4591007)	1 (4.2)	1 (2.8)	2 (3.3)	1 (4.2)	5 (13.9)	6 (10.0)
1-Month post–Dose 4 (C4591048)/post–Dose 3 (C4591007) blood draw outside of window (28-42 days after Dose 4/Dose 3)	1 (4.2)	1 (2.8)	2 (3.3)	1 (4.2)	5 (13.9)	6 (10.0)

Note: Subset of Substudy B Group 2 includes the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
a. n = number of participants with the specified characteristic
b. This value is the denominator for the percentage calculations.
c. Participants with no serological or virological evidence of past SARS-CoV-2 infection up to 1-month post–Dose 4 (C4591048) or the 1-month post–Dose 3 (C4591007) blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 4 for C4591048 participants was defined as having a negative N-binding antibody [serum] result at Dose 4 visit and 1-month post–Dose 4 visit; a negative NAAT [nasal swab] result at Dose 4 visit, and any unscheduled visit up to the 1-month post–Dose 4 blood sample collection; and had no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 for C4591007 participants was defined as having a negative N-binding antibody [serum] result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 visits; a negative NAAT [nasal swab] result at the Dose 1, Dose 2, and Dose 3 visits and any unscheduled visit up to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
d. Participants may have been excluded for more than 1 reason.
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Output File: ./nda2_ubped2/C4591048_B_1MPD_Group2_1007_IMM/adva_s008_p2_6m5y

- **Recruitment**

The study intends to recruit 300 participants. In current analysis, the first 60 subjects are analysed. The original protocol is signed for 19 August 2022. The cut-off date for data was 25 November 2022.

- **Conduct of the study**

The protocol has been amended twice until now.

Document	Version Date
Amendment 2	18 Nov 2022
Amendment 1	21 Oct 2022
Original protocol	19 Aug 2022

The amendment 2 targeted Substudy C. Protocol amendment 1 is in response to the FDA feedback received on 23 Sep 2022. This feedback requested changes to generate more data on the bivalent vaccine. The substudy B was amended by increased sample size, updated and added objectives, estimands and endpoints to study superiority of the bivalent vaccine compared to the original vaccine in sense of inducing immune response against Omicron BA.4-5 strain and induction of non-inferior level of antibodies against reference strain.

- **Baseline data**

Table 1 Demographic Characteristics – Participants with or without evidence of infection – C4591048 subset of Substudy B Group 2 and Study C4591007 Phase 2/3 Participants -≥6 months to <5 years of age – Evaluable immunogenicity population

	Vaccine Group (as Assigned/Randomized)					
	C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg			C4591007 BNT162b2 3 µg		
	≥6 Months to <2 Years (N[a]=23) n[b] (%)	≥2 to <5 Years (N[a]=35) n[b] (%)	≥6 Months to <5 Years (N[a]=58) n[b] (%)	≥6 Months to <2 Years (N[a]=23) n[b] (%)	≥2 to <5 Years (N[a]=31) n[b] (%)	≥6 Months to <5 Years (N[a]=54) n[b] (%)
Sex						
Male	9 (39.1)	20 (57.1)	29 (50.0)	14 (60.9)	14 (45.2)	28 (51.9)
Female	14 (60.9)	15 (42.9)	29 (50.0)	9 (39.1)	17 (54.8)	26 (48.1)
Race						
White	13 (56.5)	21 (60.0)	34 (58.6)	19 (82.6)	26 (83.9)	45 (83.3)
Black or African American	1 (4.3)	2 (5.7)	3 (5.2)	1 (4.3)	0	1 (1.9)
Asian	5 (21.7)	4 (11.4)	9 (15.5)	1 (4.3)	2 (6.5)	3 (5.6)
Multiracial	4 (17.4)	8 (22.9)	12 (20.7)	2 (8.7)	3 (9.7)	5 (9.3)
Ethnicity						
Hispanic/Latino	4 (17.4)	11 (31.4)	15 (25.9)	2 (8.7)	4 (12.9)	6 (11.1)
Non-Hispanic/non-Latino	19 (82.6)	24 (68.6)	43 (74.1)	21 (91.3)	27 (87.1)	48 (88.9)
Age at the Dose 4 (C4591048)/Dose 3 (C4591007) (months/years[c])						
Mean (SD)	18.6 (3.65)	2.6 (0.77)	N/A	18.3 (3.27)	2.6 (0.75)	N/A
Median	19.0	2.0	N/A	19.0	2.0	N/A
Min, max	(12, 23)	(2, 4)	N/A	(12, 23)	(2, 4)	N/A
Time (months[d]) from last prior BNT162b2 dose to Dose 4 (C4591048)/Dose 3 (C4591007)						
n	23	35	58	23	31	54
Mean (SD)	5.9 (2.02)	6.8 (1.76)	6.5 (1.90)	6.2 (1.82)	6.8 (1.89)	6.6 (1.87)
Median	6.5	7.0	6.9	6.6	7.1	6.9
Min, max	(2.1, 8.6)	(2.2, 8.5)	(2.1, 8.6)	(2.3, 8.8)	(2.2, 9.1)	(2.2, 9.1)
≥2 to <3 Months	3 (13.0)	3 (8.6)	6 (10.3)	2 (8.7)	3 (9.7)	5 (9.3)
≥3 to <4 Months	1 (4.3)	0	1 (1.7)	0	2 (6.5)	2 (3.7)
≥4 to <5 Months	3 (13.0)	2 (5.7)	5 (8.6)	3 (13.0)	0	3 (5.6)
≥5 to <6 Months	3 (13.0)	2 (5.7)	5 (8.6)	4 (17.4)	0	4 (7.4)
≥6 to <7 Months	6 (26.1)	10 (28.6)	16 (27.6)	7 (30.4)	6 (19.4)	13 (24.1)
≥7 to <8 Months	1 (4.3)	7 (20.0)	8 (13.8)	2 (8.7)	10 (32.3)	12 (22.2)
≥8 to <9 Months	6 (26.1)	11 (31.4)	17 (29.3)	5 (21.7)	8 (25.8)	13 (24.1)
≥9 Months	0	0	0	0	2 (6.5)	2 (3.7)
Time (days) from last prior BNT162b2 dose to Dose 4 (C4591048)/Dose 3 (C4591007)						
n	23	35	58	23	31	54
Mean (SD)	166.6 (56.68)	190.4 (49.34)	180.9 (53.20)	174.4 (50.93)	191.6 (52.99)	184.3 (52.35)

Median	181.0	196.0	193.5	184.0	200.0	194.0
Min, max	(60, 240)	(62, 239)	(60, 240)	(63, 246)	(62, 254)	(62, 254)
60-240 Days	23 (100.0)	35 (100.0)	58 (100.0)	22 (95.7)	28 (90.3)	50 (92.6)
>240 Days	0	0	0	1 (4.3)	3 (9.7)	4 (7.4)
Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 status						
Positive[e]	9 (39.1)	7 (20.0)	16 (27.6)	9 (39.1)	6 (19.4)	15 (27.8)
Negative[f]	13 (56.5)	28 (80.0)	41 (70.7)	13 (56.5)	23 (74.2)	36 (66.7)
Missing	1 (4.3)	0	1 (1.7)	1 (4.3)	2 (6.5)	3 (5.6)
Comorbidities[g]						
Yes	1 (4.3)	4 (11.4)	5 (8.6)	0	0	0
No	22 (95.7)	31 (88.6)	53 (91.4)	23 (100.0)	31 (100.0)	54 (100.0)

Abbreviations: BMI = body mass index; N/A = not applicable; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subset of Substudy B Group 2 includes the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. The participant age at the study vaccination is in months for the age group ≥6 months to <2 years and in years for the age groups ≥2 years to <5 years.
d. Month was calculated as 28 days.
e. For C4591048 Substudy B Group 2: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.
f. For C4591048 Substudy B Group 2: negative N-binding antibody result at Dose 4 visit, negative NAAT result at Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to Dose 3 visit, and no medical history of COVID-19.
g. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR Morb Mortal Wkly Rep. 2020;69(32):1081-8 and/or obesity (BMI ≥95th percentile) for participants of ≥2 years to <5 years. Comorbidities were assessed at the first study visit for both studies.
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- **Numbers analysed**

Numbers analysed	6m-<2 yoa	2 to 5 yoa	Total 6m-5y
Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 1.5/1.5 µg	23	35	58
C4591007 Original 3 µg	23	31	54

- **Outcomes and estimation**

Geometric Mean Titers

Omicron BA.4/BA.5 Neutralization

Participants without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of infection, the GMTs against the Omicron BA.4/BA.5 variant were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (prevaccination, 86.6; post dose, 1146.6) compared with that in the BNT162b2 group (prevaccination, 37.5; post dose, 401.3) at prevaccination and more substantially at 1-month post dose (*Table 3*). Among participants ≥6 months to <2 years of age and ≥2 to <5 years of age, a similar trend as above was observed (*Table 2*).

Participants with or without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of infection, the GMTs at prevaccination and 1-month post dose were higher in participants

who had evidence of prior SARS-CoV-2 infection (baseline positive) compared with those without evidence of prior SARS-CoV-2 infection (baseline negative) in both vaccine groups (*Table 2*).

Within both baseline positive and baseline negative groups, the GMTs against the Omicron BA.4/BA.5 variant were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with that in the BNT162b2 group at prevaccination and more substantially at 1-month post dose (*Table 3*). The similar trend was also observed among participants ≥6 months to <2 years of age and ≥2 to <5 years of age (*Table 2*).

Reference Strain Neutralization

Participants without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of infection, the GMTs against the reference strain were higher at prevaccination and similar at 1-month post dose in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (prevaccination, 2090.1 and post dose, 9253.1) compared with that in the BNT162b2 group (prevaccination, 412.6 and post dose, 8341.2) (*Table 2*). The similar trend was also observed among participants ≥6 months to <2 years of age and ≥2 to <5 years of age (*Table 2*).

Participants with or without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of infection, similar to Omicron BA.4/BA.5 neutralizing GMTS, reference strain GMTs at prevaccination and 1-month post dose were higher in participants who were baseline positive compared with those who were baseline negative in both vaccine groups (*Table 2*).

Within both the baseline positive and negative groups, the observed GMTs against the reference strain were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) compared with that in the BNT162b2 group at prevaccination (*Table 2*). At 1-month post dose, the observed GMTs were lower in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) compared with that in the BNT162b2 group within the baseline positive group; within the baseline negative group, the observed GMTs were similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and the BNT162b2 groups.

A similar trend was also observed within the baseline positive and baseline negative groups among participants ≥2 to <5 years of age and within the baseline negative group among participants ≥6 months to <2 years of age (*Table 2*).

Within the baseline positive group among participants ≥6 months to <2 years of age, the GMTs against the reference strain were similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups at prevaccination (*Table 2*). At 1-month post dose, the trend was similar to that observed within baseline positive groups among participants ≥6 months to <5 years of age and ≥2 to <5 years of age discussed above.

Table 2. Geometric Mean Titers, by Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status – C4591048 Subset of Substudy B Group 2 (at Dose 4 and 1 month after dose 4) and C4591007 Phase 2/3 Participants (at Dose 3 and 1 month after dose 3) – Participants with or without evidence of infection - ≥6 months to <5 years of age – evaluable immunogenicity population

				Vaccine Group (as Assigned/Randomized)			
				C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg		C4591007 BNT162b2 3 µg	
Assay	Age Group	Baseline (Dose 4 C4591048/ Dose 3 C4591007) SARS-CoV-2 status	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	≥6 Months to <5 Years	Overall	Prevax	54	192.5 (120.4, 307.8)	54	70.5 (51.1, 97.2)
			1 Month	58	1695.2 (1151.8, 2494.9)	54	607.9 (431.1, 857.2)
		Positive[d]	Prevax	16	1315.4 (789.1, 2192.8)	15	351.7 (195.2, 633.8)
			1 Month	16	4897.7 (3085.5, 7774.1)	15	1785.9 (1009.4, 3159.9)
		Negative[e]	Prevax	38	85.7 (56.6, 129.8)	36	38.2 (34.2, 42.8)
			1 Month	41	1116.0 (701.3, 1776.1)	36	416.2 (287.8, 602.0)
	≥6 Months to <2 Years	Overall	Prevax	21	243.9 (115.3, 516.1)	23	96.0 (55.3, 166.8)
			1 Month	23	2011.4 (1141.3, 3544.9)	23	625.6 (365.7, 1070.5)
		Positive[d]	Prevax	9	1157.5 (653.8, 2049.2)	9	368.1 (189.1, 716.9)
			1 Month	9	4978.7 (3844.4, 6447.8)	9	1378.6 (568.4, 3343.3)
		Negative[e]	Prevax	12	75.9 (39.5, 145.7)	13	40.9 (30.0, 55.7)
			1 Month	13	1074.7 (454.2, 2543.0)	13	351.3 (186.4, 662.4)
	≥2 to <5 Years	Overall	Prevax	33	165.6 (88.3, 310.5)	31	56.1 (38.0, 82.7)
			1 Month	35	1514.9 (882.2, 2601.5)	31	595.0 (370.5, 955.6)
		Positive[d]	Prevax	7	1550.5 (498.2, 4825.5)	6	328.4 (75.7, 1424.1)
			1 Month	7	4795.4 (1421.9, 16172.9)	6	2633.3 (1212.8, 5717.8)
		Negative[e]	Prevax	26	90.7 (52.1, 157.9)	23	36.8 (34.2, 39.6)
			1 Month	28	1135.7 (630.3, 2046.5)	23	458.1 (281.6, 745.1)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	≥6 Months to <5 Years	Overall	Prevax	57	2678.1 (1913.0, 3749.2)	53	776.8 (536.4, 1125.0)
			1 Month	58	9733.0 (7708.2, 12289.6)	53	9057.3 (7223.4, 11356.8)
		Positive[d]	Prevax	16	5692.3 (3206.9, 10103.6)	15	3806.2 (2339.5, 6192.4)

		1 Month	16	10659.2 (6612.0, 17183.9)	15	13024.3 (8318.8, 20391.3)
	Negative[e]	Prevax	41	1995.4 (1355.6, 2937.2)	35	417.8 (302.7, 576.7)
		1 Month	41	9336.0 (7023.1, 12410.5)	35	8131.1 (6238.2, 10598.4)
≥6 Months to <2 Years	Overall	Prevax	22	2491.2 (1432.0, 4333.8)	22	981.6 (503.5, 1913.7)
		1 Month	23	8737.2 (5959.6, 12809.5)	23	9221.7 (6734.0, 12628.3)
	Positive[d]	Prevax	9	4005.8 (1612.3, 9953.0)	9	4026.9 (2343.3, 6920.1)
		1 Month	9	8696.2 (4102.8, 18432.5)	9	11589.2 (5807.3, 23127.8)
	Negative[e]	Prevax	13	1793.0 (853.7, 3766.1)	12	363.8 (181.1, 730.8)
		1 Month	13	8525.7 (4988.2, 14572.1)	13	7751.6 (5407.5, 11111.9)
≥2 to <5 Years	Overall	Prevax	35	2802.7 (1795.7, 4374.3)	31	657.9 (421.5, 1026.9)
		1 Month	35	10448.3 (7685.1, 14205.1)	30	8933.3 (6388.0, 12492.9)
	Positive[d]	Prevax	7	8942.8 (4352.3, 18374.9)	6	3497.6 (1031.2, 11863.2)
		1 Month	7	13847.7 (6795.9, 28216.6)	6	15516.7 (7495.6, 32121.4)
	Negative[e]	Prevax	28	2097.0 (1295.2, 3395.0)	23	449.1 (309.5, 651.7)
		1 Month	28	9737.9 (6811.7, 13921.2)	22	8364.0 (5685.0, 12305.6)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subset of Substudy B Group 2 includes the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
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 titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. For C4591048 Substudy B Group 2: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.
e. For C4591048 Substudy B Group 2: negative N-binding antibody result at Dose 4 visit, negative NAAT result at Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 11JAN2023 (00:33)
(Data cutoff date: C4591048 Substudy B[25NOV2022]/C4591007[07AUG2022])
Output File: ./nda2_ubped2/C4591048_B_1MPD_Group2_1007_IMM/adva_s001_p2_6m5y_evl

Geometric Mean Fold Rises

Omicron BA.4/BA.5 Neutralization

Participants without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of infection, for the Omicron BA.4/BA.5 variant, the GMFRs were similar in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group (13.6 [95% CI: 8.4, 21.9]) compared with that in the BNT162b2 group (10.7 [95% CI: 7.3, 15.8]) at 1-month post dose (*Table 3*).

Among participants ≥6 months to <2 years of age and ≥2 to <5 years of age, a similar trend as above was observed (*Table 3*).

Participants with or without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of infection, the GMFRs at 1-month post dose were lower in participants who were baseline positive compared with those who were baseline negative in both vaccine groups (*Table 3*

Within baseline positive and baseline negative groups, the GMFRs were similar in the bivalent BNT162b2 Original/Omi BA.4/BA.5 and BNT162b2 groups at 1-month post dose (*Table 3*).

Among participants ≥6 months to <2 years of age, the GMFRs were similar in the bivalent BNT162b2 Original/Omi BA.4/BA.5 and BNT162b2 groups at 1-month post dose within the baseline positive group; within the baseline negative group, the observed GMFRs were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with that in the BNT162b2 group (*Table 3*). Among participants ≥2 to <5 years of age, the observed GMFRs were lower in the bivalent BNT162b2 Original/Omi BA.4/BA.5 compared with the BNT162b2 group at 1-month post dose within the baseline positive group; within the baseline negative group, the GMFRs were similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups.

Reference Strain Neutralization

Participants without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of infection, for the reference strain, the GMFRs were lower in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group (4.4 [95% CI: 3.1, 6.3]) compared with that in the BNT162b2 group (19.8 [95% CI: 13.4, 29.2]) at 1-month post dose (*Table 3*). The lower GMFRs in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group were likely due to the much higher prevaccination titers in this group compared with the BNT162b2 group.

Among participants ≥6 months to <2 years of age and ≥2 to <5 years of age, a similar trend as above was observed (*Table 3*).

Participants with or without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of infection, the GMFRs at 1-month post dose were lower in participants who were baseline positive compared with those who were baseline negative in both vaccine groups (Table 3).

At 1-month post dose, within the baseline positive group, the observed GMFRs were slightly lower in the bivalent BNT162b2 Original/Omi BA.4/BA.5 compared with that in the BNT162b2 group (*Table 3*). A similar trend was also observed in participants ≥2 to 5 years of age. For participants ≥6 months to <2 years of age, the GMFRs were similar in the bivalent BNT162b2 Original/Omi BA.4/BA.5 and BNT162b2 groups.

Within the baseline negative group, among participants ≥6 months to <5 years of age, the GMFRs were lower in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group compared with that in the BNT162b2 group (Table 3). A similar trend was also observed among participants ≥6 months to <2 years of age and ≥2 to <5 years of age.

Table 3

Geometric Mean Fold Rises, by Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status – C4591048 Subset of Substudy B Group 2 (From Dose 4 to 1 Month After Dose 4) and C4591007 Phase 2/3 Participants (From Dose 3 to 1 Month After Dose 3) – Participants With or Without Evidence of Infection – ≥6 Months to <5 Years of Age – Evaluable Immunogenicity Population

				Vaccine Group (as Assigned/Randomized)			
				C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg		C4591007 BNT162b2 3 µg	
Assay	Age Group	Baseline (Dose 4 C4591048/ Dose 3 C4591007) SARS-CoV-2 status	Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	≥6 Months to <5 Years	Overall	1 Month	54	9.1 (6.3, 13.3)	54	8.6 (6.3, 11.7)
		Positive[d]	1 Month	16	3.7 (2.2, 6.2)	15	5.1 (2.8, 9.1)
		Negative[e]	1 Month	38	13.3 (8.5, 20.7)	36	10.9 (7.5, 15.8)
	≥6 Months to <2 Years	Overall	1 Month	21	8.2 (4.8, 13.9)	23	6.5 (4.2, 10.2)
		Positive[d]	1 Month	9	4.3 (2.5, 7.4)	9	3.7 (2.1, 6.7)
		Negative[e]	1 Month	12	13.4 (6.2, 29.0)	13	8.6 (4.6, 16.1)
	≥2 to <5 Years	Overall	1 Month	33	9.7 (5.7, 16.6)	31	10.6 (6.9, 16.3)
		Positive[d]	1 Month	7	3.1 (1.0, 10.0)	6	8.0 (1.9, 33.0)
		Negative[e]	1 Month	26	13.2 (7.4, 23.7)	23	12.5 (7.6, 20.3)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	≥6 Months to <5 Years	Overall	1 Month	57	3.6 (2.7, 4.8)	52	11.4 (8.1, 16.1)
		Positive[d]	1 Month	16	1.9 (1.2, 2.8)	15	3.4 (2.1, 5.5)
		Negative[e]	1 Month	41	4.7 (3.3, 6.6)	34	19.1 (13.2, 27.5)
	≥6 Months to <2 Years	Overall	1 Month	22	3.5 (2.1, 5.7)	22	9.1 (5.1, 16.2)
		Positive[d]	1 Month	9	2.2 (1.2, 3.9)	9	2.9 (2.0, 4.1)
		Negative[e]	1 Month	13	4.8 (2.3, 10.0)	12	19.8 (9.8, 40.0)
	≥2 to <5 Years	Overall	1 Month	35	3.7 (2.6, 5.4)	30	13.4 (8.6, 21.0)
		Positive[d]	1 Month	7	1.5 (0.7, 3.2)	6	4.4 (1.2, 16.3)
		Negative[e]	1 Month	28	4.6 (3.1, 7.0)	22	18.6 (11.7, 29.7)

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subset of Substudy B Group 2 includes the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay both before Dose 4 (C4591048)/Dose 3 (C4591007) and at the given sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. For C4591048 Substudy B Group 2: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.
e. For C4591048 Substudy B Group 2: negative N-binding antibody result at Dose 4 visit, negative NAAT result at Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 11JAN2023 (00:33)
(Data cutoff date: C4591048 Substudy B[25NOV2022]/C4591007[07AUG2022])
Output File: ./nda2_ubped2/C4591048_B_1MPD_Group2_1007_IMM/adva_s002_p2_6m5y_ev1

Seroresponse rates

Omicron BA.4/BA.5 Neutralization

Participants without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of infection, 27 (77.1%) participants in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group and 21 (61.8%) participants in the BNT162b2 group achieved seroresponse against the Omicron BA.4/BA.5 variant at 1-month post dose (Table 6).

Among participants ≥6 months to <2 years of age, 9 (81.8%) and 6 (46.2%) participants in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group and the BNT162b2 group, respectively, achieved seroresponse against the Omicron BA.4/BA.5 variant. A total of 18 (75.0%) and 15 (71.4%) participants ≥2 to <5 years of age in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group and the BNT162b2 group, respectively, achieved seroresponse against the Omicron BA.4/BA.5 variant.

Participants with or without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of infection, within the baseline positive group, 9 (56.3%) participants in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group and 9 (60.0%) participants in the BNT162b2 group achieved seroresponse against the Omicron BA.4/BA.5 variant at 1-month post dose (***Table 4***). Within the baseline negative group, 29 (76.3%) and 23 (63.9%) participants in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group and BNT162b2 group, respectively, achieved seroresponse.

Among participants ≥6 months to <2 years of age and those ≥2 to <5 years of age, the percentages of participants who achieved seroresponse are provided in ***Table 4***.

Reference Strain Neutralization

Participants without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of infection, 20 (52.6%) participants in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group and 29 (90.6%) participants in the BNT162b2 group achieved seroresponse against the reference strain at 1-month post dose (Table 6). The lower percentage of participants achieving seroresponse in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group was likely a reflection of the higher prevaccination titers in this group compared with the BNT162b2 group.

Among participants ≥6 months to <2 years of age, 6 (50.0%) and 11 (91.7%) participants in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group and the BNT162b2 group, respectively, achieved seroresponse against the reference strain. A total of 14 (53.8%) and 18 (90.0%) participants ≥2 to <5 years of age in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group and the BNT162b2 group, respectively, achieved seroresponse against the reference strain (***Table 4***).

Participants with or without evidence of infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of infection, the percentages of participants who achieved seroresponse were lower in the baseline positive group compared with those in the baseline negative group in both vaccine groups (***Table 4***).

Within the baseline positive group, 3 (18.8%) participants in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group and 5 (33.3%) participants in the BNT162b2 group achieved seroresponse against the reference strain at 1-month post dose (***Table 4***). Within the baseline negative group, 22 (53.7%) and 31 (91.2%) participants in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group and BNT162b2 group, respectively, achieved seroresponse. The lower percentage of participants achieving seroresponse in the bivalent BNT162b2 Original/Omi BA.4/BA.5 group was likely a reflection of the higher prevaccination titers in this group compared with the BNT162b2 group.

Among participants ≥6 months to <2 years of age and those ≥2 to <5 years of age, the percentages of participants who achieved seroresponse are provided in ***Table 4***.

Table 4

Number (%) of Participants With Seroresponse, by Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status– C4591048 Subset of Substudy B Group 2 (1 Month After Dose 4) and C4591007 Phase 2/3 Participants (1 Month After Dose 3) – Participants With or Without Evidence of Infection – ≥6 Months to <5 Years of Age – Evaluable Immunogenicity Population

				Vaccine Group (as Assigned/Randomized)			
				C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg		C4591007 BNT162b2 3 µg	
Assay	Age Group	Baseline (Dose 4 C4591048/ Dose 3 C4591007) SARS-CoV-2 status	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	≥6 Months to <5 Years	Overall	1 Month	54	38 (70.4) (56.4, 82.0)	54	33 (61.1) (46.9, 74.1)
		Positive[e]	1 Month	16	9 (56.3) (29.9, 80.2)	15	9 (60.0) (32.3, 83.7)
		Negative[f]	1 Month	38	29 (76.3) (59.8, 88.6)	36	23 (63.9) (46.2, 79.2)
	≥6 Months to <2 Years	Overall	1 Month	21	14 (66.7) (43.0, 85.4)	23	11 (47.8) (26.8, 69.4)
		Positive[e]	1 Month	9	5 (55.6) (21.2, 86.3)	9	4 (44.4) (13.7, 78.8)
		Negative[f]	1 Month	12	9 (75.0) (42.8, 94.5)	13	6 (46.2) (19.2, 74.9)
	≥2 to <5 Years	Overall	1 Month	33	24 (72.7) (54.5, 86.7)	31	22 (71.0) (52.0, 85.8)
		Positive[e]	1 Month	7	4 (57.1) (18.4, 90.1)	6	5 (83.3) (35.9, 99.6)
		Negative[f]	1 Month	26	20 (76.9) (56.4, 91.0)	23	17 (73.9) (51.6, 89.8)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	≥6 Months to <5 Years	Overall	1 Month	57	25 (43.9) (30.7, 57.6)	52	39 (75.0) (61.1, 86.0)
		Positive[e]	1 Month	16	3 (18.8) (4.0, 45.6)	15	5 (33.3) (11.8, 61.6)
		Negative[f]	1 Month	41	22 (53.7) (37.4, 69.3)	34	31 (91.2) (76.3, 98.1)
	≥6 Months to <2 Years	Overall	1 Month	22	9 (40.9) (20.7, 63.6)	22	13 (59.1) (36.4, 79.3)
		Positive[e]	1 Month	9	2 (22.2) (2.8, 60.0)	9	1 (11.1) (0.3, 48.2)
		Negative[f]	1 Month	13	7 (53.8) (25.1, 80.8)	12	11 (91.7) (61.5, 99.8)
	≥2 to <5 Years	Overall	1 Month	35	16 (45.7) (28.8, 63.4)	30	26 (86.7) (69.3, 96.2)
		Positive[e]	1 Month	7	1 (14.3) (0.4, 57.9)	6	4 (66.7) (22.3, 95.7)
		Negative[f]	1 Month	28	15 (53.6) (33.9, 72.5)	22	20 (90.9) (70.8, 98.9)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subset of Substudy B Group 2 includes the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
Note: For participants from C4591048 Substudy B Group 2, seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥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 both before Dose 4 (C4591048)/Dose 3 (C4591007) and at the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. For C4591048 Substudy B Group 2: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.
f. For C4591048 Substudy B Group 2: negative N-binding antibody result at Dose 4 visit, negative NAAT result at Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 11JAN2023 (00:33)
(Data cutoff date: C4591048 Substudy B[25NOV2022]/C4591007[07AUG2022])
Output File: ./nda2_ubped2/C4591048_B_1MPD_Group2_1007_IMM/adva_s003_p2_6m5y_ev1

- **Ancillary analyses**

Neutralization of Omicron sublineages

The MAH submitted additionally 1-month postdose immunogenicity data for Omicron sublineages XBB.1.5, BQ.1.1, and BA.4/BA.5 in a subset of 31 participants ≥6 months to <5 years of age in Group 2 of C4591048 Substudy B who received a fourth dose with 3 µg of the bivalent BNT162b2 (Original/Omi BA.4/BA.5) vaccine and a comparator subset of 31 participants in Study C4591007 Phase 2/3 who received 3 doses at 3 µg each of original BNT162b2.

Selection of participants for additional neutralization testing

Participants in these analyses were among the first 60 assigned participants in C4591048 Substudy B Group 2 and the corresponding comparator group of 60 participants (subset from C4591007 Phase 2/3) who had sufficient sample volume remaining for the additional neutralization testing.

The participants in the comparator group were matched by age, prior SARS-CoV-2 infection status (before Dose 4 for participants in C4591048 Substudy B and before Dose 3 for participants in C4591007 Phase 2/3), and dosing interval (between Dose 3 and Dose 4 for participants in C4591048 Substudy B and between Dose 2 and Dose 3 for participants in C4591007 Phase 2/3) with this subset of participants in C4591048 Substudy B. Participants in C4591048 Substudy B Group 2 received Dose 4 (booster) with bivalent BNT162b2 (Original/Omi BA.4/BA.5) in September-October 2022 and participants in the comparator group from C4591007 Phase 2/3 received Dose 3 of original BNT162b2 in February-July 2022.

Immunogenicity Endpoints and Analysis Methods
Descriptive immunogenicity analyses were performed to characterize Omicron XBB.1.5, BQ.1.1, and BA.4/BA.5 neutralization responses following a fourth dose with bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg or following 3 doses at 3 µg each of original BNT162b2. A non-validated recombinant SARS-CoV-2 FFRNT was used to determine Omicron XBB.1.5, BQ.1.1, and BA.4/BA.5 neutralizing titers.
GMTs and GMFRs with 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and fold rises, respectively, and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
Seroresponse was defined as achieving a ≥4-fold rise from baseline (before the first study vaccination [fourth dose]). If the baseline measurement was below the LLOQ, the postvaccination measure of ≥4 × LLOQ was considered seroresponse.

Immunogenicity Results

Immunogenicity population

In the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group, the evaluable immunogenicity population (with or without evidence of infection up to 1-month post-Dose 4) included 30 (96.8%) participants ≥6 months to <5 years of age. In the comparator group, the numbers of participants in the evaluable immunogenicity population with or without evidence of infection up to 1-month post-Dose 3 included 27 (87.1%) participants ≥6 months to <5 years of age

Demographics

In the evaluable immunogenicity population with or without evidence of infection, 10 (33.3%) participants in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group had evidence of prior SARS-CoV-2 infection ("baseline positive") at the time of study vaccination (Dose 4). Median time since last dose of BNT162b2 before study vaccination (Dose 4) was 7.0 months in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group. In the BNT162b2 group, 33.3% of participants were baseline positive prior to Dose 3. Median time between Dose 2 and Dose 3 of BNT162b2 was 7.0 months in the BNT162b2 group.

GMTs

Omicron XBB.1.5

Participants with or without evidence of prior infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of prior SARS-CoV-2 infection, the observed GMTs against Omicron XBB.1.5 were higher in participants who were baseline positive compared with those who were baseline negative in both vaccine groups at prevaccination and at 1-month postdose (*Table 5*).

Within baseline positive participants, GMTs against Omicron XBB.1.5 were similar at prevaccination and higher at 1-month postdose in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) compared with the BNT162b2 group (*Table 5*).

Within baseline negative participants, GMTs against Omicron XBB.1.5 were similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups at both prevaccination and at 1-month postdose (*Table 5*).

GMTs against Omicron XBB.1.5 were lower or similar at prevaccination and lower at 1-month postdose compared with GMTs against BA.4/BA.5 within baseline positive and baseline negative participants in both vaccine groups (*Table 5*).

Participants without evidence of prior infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection:

-The observed GMTs against Omicron XBB.1.5 were similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group at both prevaccination and 1-month postdose (*Table 5*).

- In both groups, GMTs against Omicron XBB.1.5 were lower compared with GMTs against BA.4/BA.5 at 1-month postdose

Omicron BQ.1.1

Participants with or without evidence of prior infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of prior SARS-CoV-2 infection, the observed GMTs against Omicron BQ.1.1 were higher in participants who were baseline positive compared with those who were baseline negative in both vaccine groups (***Table 5***).

Within both baseline positive and negative participants, GMTs against Omicron BQ.1.1 were similar at prevaccination and higher at 1-month postdose in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) compared with the BNT162b2 group (***Table 5***).

GMTs against Omicron BQ.1.1 were lower or similar at prevaccination and lower at 1-month postdose compared with GMTs against BA.4/BA.5 within baseline positive and baseline negative participants in both vaccine groups (***Table 5***).

Participants without evidence of prior infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection:

-The observed GMTs against Omicron BQ.1.1 were similar at prevaccination and higher at 1-month postdose in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group (***Table 5***).

-In both vaccine groups, GMTs against Omicron BQ.1.1 were lower compared with GMTs against BA.4/BA.5 at 1-month postdose (***Table 5***).

Table 5.

Geometric Mean Titers, by Baseline SARS-CoV-2 Status – New Variants Neutralization – C4591048 Subset of Substudy B Group 2 (at Dose 4 and 1 Month After Dose 4) and C4591007 Phase 2/3 Participants (at Dose 3 and 1 Month After Dose 3) – ≥6 Months to <5 Years of Age – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

			Vaccine Group (as Assigned/Randomized)			
			C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg		C4591007 BNT162b2 3 µg	
Assay	Baseline (Dose 4 C4591048/ Dose 3 C4591007) SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron XBB.1.5 - NT50 (titer)	Overall	Prevax	30	14.6 (11.3, 19.0)	27	12.0 (10.4, 13.8)
		1 Month	30	37.3 (24.6, 56.6)	27	20.3 (15.5, 26.5)
	Positive[d]	Prevax	10	22.2 (13.9, 35.4)	9	17.1 (12.0, 24.5)
		1 Month	10	88.8 (40.9, 192.8)	9	38.5 (27.4, 54.0)
	Negative[e]	Prevax	20	11.9 (8.9, 16.0)	17	10.0 (10.0, 10.0)
		1 Month	20	24.2 (16.1, 36.3)	17	15.0 (11.3, 20.0)
SARS-CoV-2 FFRNT - Omicron BQ.1.1 - NT50 (titer)	Overall	Prevax	30	19.3 (13.2, 28.2)	27	14.3 (11.5, 17.9)
		1 Month	30	84.8 (54.5, 131.9)	27	27.2 (20.5, 36.2)
	Positive[d]	Prevax	10	38.6 (21.7, 68.9)	9	29.4 (22.2, 38.9)
		1 Month	10	234.3 (136.3, 402.5)	9	56.6 (40.8, 78.4)

	Negative[e]	Prevax	20	13.7 (8.8, 21.2)	17	10.0 (10.0, 10.0)
		1 Month	20	51.0 (31.6, 82.4)	17	18.8 (14.2, 25.0)
SARS-CoV-2 FFRNT - Omicron BA.4/BA.5 - NT50 (titer)	Overall	Prevax	30	54.0 (31.2, 93.4)	27	25.9 (15.4, 43.5)
		1 Month	30	432.1 (247.3, 755.1)	27	138.9 (94.6, 204.1)
	Positive[d]	Prevax	10	211.1 (122.3, 364.4)	9	148.1 (92.0, 238.5)
		1 Month	10	1575.9 (876.4, 2833.5)	9	332.6 (193.8, 570.8)
	Negative[e]	Prevax	20	27.3 (15.3, 48.8)	17	10.8 (9.6, 12.2)
		1 Month	20	226.3 (121.4, 421.8)	17	90.4 (59.8, 136.6)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subset of Substudy B Group 2 for new variants neutralization includes participants who have sufficient blood volume for variant of concerns assay testing among the first 24 and 36 participants assigned in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
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 titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. For C4591048 Substudy B Group 2: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.
e. For C4591048 Substudy B Group 2: negative N-binding antibody result at Dose 4 visit, negative NAAT result at Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16MAR2023 (03:16)
(Data cutoff date: C4591048 Substudy B[30NOV2022]/C4591007[07AUG2022])
Output File: ./nda2_ubped2/C4591048_B_GP2_145_1MPD_Immunobridging/adva_s001_p2_6m5y_evl

GMFRs

Omicron XBB.1.5

Participants with or without evidence of prior infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of prior SARS-CoV-2 infection, the observed GMFRs of neutralizing titers from before study vaccination to 1-month postdose for Omicron XBB.1.5 were higher in participants who were baseline positive compared with those who were baseline negative in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (*Table 6*). In the BNT162b2 group, the observed GMFRs of Omicron XBB.1.5-neutralizing titers were similar in participants who were baseline positive and those who were baseline negative.

Within baseline positive participants, from before study vaccination to 1-month postdose, GMFRs of neutralizing titers for Omicron XBB.1.5 were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group (***Table 6***).

Within baseline negative participants, from before study vaccination to 1-month postdose, GMFRs of neutralizing titers for Omicron XBB.1.5 were similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group (***Table 6***).

GMFRs against Omicron XBB.1.5 were lower or similar compared with GMFRs against BA.4/BA.5 within baseline positive and baseline negative participants in both vaccine groups (***Table 6***).

Participants without evidence of prior infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, from before study vaccination to 1-month postdose,

-GMFRs of neutralizing titers for Omicron XBB.1.5 were similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 (***Table 6***).

-In both vaccine groups, GMFRs against Omicron XBB.1.5 were lower compared with GMFRs against Omicron BA.4/BA.5.

Omicron BQ.1.1

Participants with or without evidence of prior infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of prior SARS-CoV-2 infection, the observed GMFRs of neutralizing titers from before study vaccination to 1-month postdose for Omicron BQ.1.1 were higher in participants who were baseline positive compared with those who were baseline negative in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (*Table 6*). In the BNT162b2 group, the observed GMFRs of Omicron BQ.1.1-neutralizing titers were similar in participants who were baseline positive and those who were baseline negative.

Within both baseline positive and baseline negative participants, from before study vaccination to 1-month postdose, GMFRs of neutralizing titers for Omicron BQ.1.1 were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group (***Table 6***).

GMFRs against Omicron BQ.1.1 were lower or similar compared with GMFRs against BA.4/BA.5 within baseline positive and baseline negative participants in both vaccine groups.

Participants without evidence of prior infection

Among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, from before study vaccination to 1-month postdose,

-GMFRs of neutralizing titers for Omicron BQ.1.1 were slightly higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group.

-In both vaccine groups, GMFRs against Omicron BQ.1.1 were lower compared with GMFRs against Omicron BA.4/BA.5

Table 6.

Geometric Mean Fold Rises, by Baseline SARS-CoV-2 Status – New Variants Neutralization – C4591048 Subset of Substudy B Group 2 (From Dose 4 to 1 Month After Dose 4) and C4591007 Phase 2/3 Participants (From Dose 3 to 1 Month After Dose 3) – ≥6 Months to <5 Years of Age – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

			Vaccine Group (as Assigned/Randomized)			
			C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg		C4591007 BNT162b2 3 µg	
Assay	Baseline (Dose 4 C4591048/ Dose 3 C4591007) SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron XBB.1.5 - NT50 (titer)	Overall	1 Month	30	2.5 (1.8, 3.6)	27	1.7 (1.4, 2.1)
	Positive[d]	1 Month	10	4.0 (1.8, 9.1)	9	2.2 (1.6, 3.1)
	Negative[e]	1 Month	20	2.0 (1.4, 2.9)	17	1.5 (1.1, 2.0)
SARS-CoV-2 FFRNT - Omicron BQ.1.1 - NT50 (titer)	Overall	1 Month	30	4.4 (3.2, 6.0)	27	1.9 (1.6, 2.3)
	Positive[d]	1 Month	10	6.1 (3.5, 10.5)	9	1.9 (1.4, 2.7)
	Negative[e]	1 Month	20	3.7 (2.5, 5.5)	17	1.9 (1.4, 2.5)
SARS-CoV-2 FFRNT - Omicron BA.4/BA.5 - NT50 (titer)	Overall	1 Month	30	8.0 (5.2, 12.3)	27	5.4 (3.7, 7.7)
	Positive[d]	1 Month	10	7.5 (4.2, 13.4)	9	2.2 (1.5, 3.3)
	Negative[e]	1 Month	20	8.3 (4.5, 15.3)	17	8.3 (5.6, 12.4)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subset of Substudy B Group 2 for new variants neutralization includes participants who have sufficient blood volume for variant of concerns assay testing among the first 24 and 36 participants assigned in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay both before Dose 4 (C4591048)/Dose 3 (C4591007) and at the given sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. For C4591048 Substudy B Group 2: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.
e. For C4591048 Substudy B Group 2: negative N-binding antibody result at Dose 4 visit, negative NAAT result at Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16MAR2023 (03:16)
(Data cutoff date: C4591048 Substudy B[30NOV2022]/C4591007[07AUG2022])
Output File: ./nda2_ubped2/C4591048_B_GP2_145_1MPD_Immunobridging/adva_s002_p2_6m5y_evl

Seroresponse rates

Omicron XBB.1.5

Participants with or without evidence of prior infection

At 1-month postdose, among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of prior SARS-CoV-2 infection, the percentage of participants with seroresponse against Omicron XBB.1.5 were higher in participants who were baseline positive compared with those who were baseline negative in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (***Table 7***). In the BNT162b2 group, 1 (11.1%) baseline positive participant and no baseline negative participant achieved seroresponse against Omicron XBB.1.5.

Within baseline positive participants, at 1-month postdose, the percentage of participants who achieved seroresponse against Omicron XBB.1.5 was higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group (***Table 7***).

Within baseline negative participants, at 1-month postdose, 2 (10.0%) participants and no participant achieved seroresponse against Omicron XBB.1.5 in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group and BNT162b2 group, respectively (***Table 7***).

The percentage of participants who achieved seroresponse against Omicron XBB.1.5 was generally lower compared with participants who achieved seroresponse against Omicron BA.4/BA.5 within baseline positive and negative participants in both vaccine groups (***Table 7***).

Participants without evidence of prior infection

At 1-month postdose, among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection:

-Two (11.1%) participants and no participant achieved seroresponse against Omicron XBB.1.5 in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group and BNT162b2 group, respectively (***Table 7***).

- In both vaccine groups, the percentage of participants who achieved seroresponse against Omicron XBB.1.5 was lower compared with participants who achieved seroresponse against Omicron BA.4/BA.5.

Omicron BQ.1.1

Participants with or without evidence of prior infection

At 1-month postdose, among participants ≥6 months to <5 years of age in the evaluable immunogenicity population with or without evidence of prior SARS-CoV-2 infection, the percentage of participants with seroresponse against Omicron BQ.1.1 were higher in participants who were baseline positive compared with those who were baseline negative in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (***Table 7***). In the BNT162b2 group, 1 (11.1%) baseline positive participant and no baseline negative participant achieved seroresponse against Omicron BQ.1.1.

Within both baseline positive and baseline negative groups, the percentage of participants who achieved seroresponse against Omicron BQ.1.1 was higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group (***Table 7***).

The percentage of participants who achieved seroresponse against Omicron BQ.1.1 was lower compared with participants who achieved seroresponse against Omicron BA.4/BA.5 within baseline positive and baseline negative participants in both vaccine groups (***Table 7***).

Participants without evidence of prior infection

At 1-month postdose, among participants ≥6 months to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection:

-The percentage of participants who achieved seroresponse against Omicron BQ.1.1 was higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group (***Table 7***).

-In both vaccine groups, the percentage of participants who achieved seroresponse against Omicron BQ.1.1 was lower compared with participants who achieved seroresponse against Omicron BA.4/BA.5.

Table 7.

Number (%) of Participants With Seroresponse, by Baseline SARS-CoV-2 Status – New Variants Neutralization – C4591048 Subset of Substudy B Group 2 (1 Month After Dose 4) and C4591007 Phase 2/3 Participants (1 Month After Dose 3) – ≥6 Months to <5 Years of Age – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

			Vaccine Group (as Assigned/Randomized)			
			C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg		C4591007 BNT162b2 3 µg	
Assay	Baseline (Dose 4 C4591048/ Dose 3 C4591007) SARS-CoV-2 Status	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 FFRNT - Omicron XBB.1.5 - NT50 (titer)	Overall	1 Month	30	8 (26.7) (12.3, 45.9)	27	1 (3.7) (0.1, 19.0)
	Positive[e]	1 Month	10	6 (60.0) (26.2, 87.8)	9	1 (11.1) (0.3, 48.2)
	Negative[f]	1 Month	20	2 (10.0) (1.2, 31.7)	17	0 (0.0) (0.0, 19.5)
SARS-CoV-2 FFRNT - Omicron BQ.1.1 - NT50 (titer)	Overall	1 Month	30	15 (50.0) (31.3, 68.7)	27	1 (3.7) (0.1, 19.0)
	Positive[e]	1 Month	10	7 (70.0) (34.8, 93.3)	9	1 (11.1) (0.3, 48.2)
	Negative[f]	1 Month	20	8 (40.0) (19.1, 63.9)	17	0 (0.0) (0.0, 19.5)
SARS-CoV-2 FFRNT - Omicron BA.4/BA.5 - NT50 (titer)	Overall	1 Month	30	20 (66.7) (47.2, 82.7)	27	17 (63.0) (42.4, 80.6)
	Positive[e]	1 Month	10	8 (80.0) (44.4, 97.5)	9	3 (33.3) (7.5, 70.1)
	Negative[f]	1 Month	20	12 (60.0) (36.1, 80.9)	17	13 (76.5) (50.1, 93.2)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subset of Substudy B Group 2 for new variants neutralization includes participants who have sufficient blood volume for variant of concerns assay testing among the first 24 and 36 participants assigned in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
Note: For participants from C4591048 Substudy B Group 2, seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥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 both before Dose 4 (C4591048)/Dose 3 (C4591007) and at the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. For C4591048 Substudy B Group 2: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.
f. For C4591048 Substudy B Group 2: negative N-binding antibody result at Dose 4 visit, negative NAAT result at Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16MAR2023 (03:16)
(Data cutoff date: C4591048 Substudy B[30NOV2022]/C4591007[07AUG2022])
Output File: ./nda2_ubped2/C4591048_B_GP2_145_1MPD_Immunobridging/adva_s003_p2_6m5y_evl

- **Summary of main efficacy results**

MAH immunogenicity conclusions for the descriptive preliminary data for Omicron BA.4-5 and Reference Strain

At 1-month post dose, a fourth dose with bivalent BNT162b2 (Original/Omi BA.4/BA.5) at 3 µg in a subset of participants ≥6 months to <5 years of age in the C4591048 Substudy B Group 2 who received 3 prior doses of BNT162b2 at 3 µg elicited

- Higher Omicron BA.4/BA.5-specific neutralizing titers compared with the titers in a comparator group of participants in C4591007 Phase 2/3 who received 3 doses of BNT162b2.
- Similar reference strain-specific titers compared with the titers in the comparator group of participants in C4591007 Phase 2/3 who received 3 doses of BNT162b2.

- The control group participants had matched prior infection status (by baseline serology [Nbinding],PCR, and medical history) to the bivalent BNT162b2 group. Given the higher prevaccination GMTs in the control group, further understanding of the sensitivity of N-binding to detect prior infection in children who overall have more asymptomatic infection and less severe disease compared with adults may need to be further explored.

These descriptive data align with the adult data and reinforce the importance of a bivalent booster dose in this age group.

MAH immunogenicity conclusions for Omicron sublineage XBB.1.5 and BQ.1.1 neutralization

At 1-month postdose, a fourth dose with bivalent BNT162b2 (Original/Omi BA.4/BA.5) at 3 µg in a subset of participants ≥6 months to <5 years of age in the C4591048 Substudy B Group 2 who received 3 prior doses of original BNT162b2 at 3 µg each elicited lower levels of neutralizing antibodies against BQ.1.1 and XBB.1.5 compared with Omicron BA.4/BA.5 neutralizing titers.

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 8. Summary of efficacy for trial C4591048 Substudy B

Title: A Master Phase 1/2/3 Protocol to Investigate the Safety, Tolerability, and Immunogenicity of Bivalent BNT162b2 RNA-Based Vaccine Candidate in Healthy Children			
Study identifier	C4591048 Substudy B		
Design	Substudy B is open-label		
	Follow-up for immunogenicity		19.08. 2022- 25.11.2022 (immunogenicity)
Hypothesis	Descriptive immunogenicity analysis for sentinel cohort		
Treatments groups Children 6m-<5 yoa	Active arm C4591048		Original/Omicron BA4-5 (1.5/1.5 µg) as 4th dose for subjects previously vaccinated with 3 doses of Original 3 µg
	Historical control arm C4591007		Original Comirnaty (3 µg), 3 doses
Endpoints and definitions	Immunogenicity endpoint	GMT	geometric mean titers (GMTs) at 1 month after Dose 4 (bivalent) or Dose 3 (Original)
	Immunogenicity endpoint	GMFR	geometric mean fold rise (GMFR) of titers (GMTs) at 1 month after last dose compared to the baseline
	Immunogenicity endpoint	Sero respon se rate	percentage of participants with a ≥4-fold rise in neutralizing titers from before vaccination to 1 month after last dose (seroresponse rate).
Database lock	25.11.2022		
Results and Analysis			

Title: A Master Phase 1/2/3 Protocol to Investigate the Safety, Tolerability, and Immunogenicity of Bivalent BNT162b2 RNA-Based Vaccine Candidate in Healthy Children			
Analysis description	**Immunogenicity Analysis**		
Analysis population and time point description	1 month after last dose Evaluable Immunogenicity population		
Effect estimate per comparison	**Treatment group**	**C4591048 4th dose with Original/Omicron (1.5/1.5 µg)**	**C4591007 3 doses with Original 3 µg**
	Omicron BA4-5 neutralization		
	Number of subject	Baseline N= 54 Post 4th dose N= 58	Baseline N= 54 Post 3rd dose N= 54
	Baseline GMT (95% CI)	192.5 (120.4, 307.8)	70.5 (51.1, 97.2)
	1m post last dose GMT (95% CI)	1695.2 (1151.8, 2494.9)	607.9 (431.1, 857.2)
	GMFR (GMT 1m post last dose/ baseline)	9.1 (6.3, 13.3)	8.6 (6.3, 11.7)
	Seroresponse rate % (95% CI)	38 out of 54 (70.4 %) (56.4, 82.0 %)	33 out of 54 (61.1 %) (46.9, 74.1 %)
Reference Strain Neutralization			
	Number of subject	Baseline N= 57 Post 4th dose N= 58	Baseline N= 53 Post 3rd dose N= 53
	Baseline GMT (95% CI)	2678.1 (1913.0, 3749.2)	776.8 (536.4, 1125.0)
	1m post last dose GMT (95% CI)	9733.0 (7708.2, 12289.6)	9057.3 (7223.4, 11356.8)
	GMFR (GMT 1m post last dose/ baseline)	3.6 (2.7, 4.8)	11.4 (8.1, 16.1)
	Seroresponse rate % (95% CI)	25 out of 57 (43.9%) (30.7, 57.6 %)	39 out of 52 (75.0 %) (61.1, 86.0 %)

2.6.2.3. Supportive studies

C4591048 Substudy D Group 2 Safety and Immunogenicity Ad Hoc Report Phase 3 (United States)	BioNTech (Pfizer)	**Primary Objectives: Primary Safety (Safety Population)** To describe the safety and tolerability profiles of prophylactic bivalent BNT162b2 given as a third or fourth dose in participants ≥5 to <12 years of age. **Primary immunogenicity** To descriptively compare the anti–Omicron BA.4/BA.5 immune response between participants ≥5 to <12 years of age who received 3 prior doses of BNT162b2 10 µg and received bivalent BNT162b2 as a fourth dose in Group 2 and Study C4591007 Phase 2/3 participants ≥5 to <12 years of age who received 3 doses of BNT162b2 10 µg. **Secondary immunogenicity** To describe the immune response elicited by bivalent BNT162b2 given as a fourth dose in participants ≥5 to <12 years of age.	**Subset of Substudy D Group 2 (4th dose)** BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 10 µg **Substudy D Group 2 (4th dose)** BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 10 µg **Study C4591007** Phase 2/3 participants ≥5 to <12 years of age who received 3 doses of BNT162b2 10 µg.	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 10 µg ≥5 years to <12 Years: N=113 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 10 µg (4th dose) ≥5 years to <12 Years: N=113 BNT162b2 Original 10 µg (3rd dose) N=113
C4591044 Cohort 2 and Combined Cohort 2 (Groups 2 & 4) + Cohort 3 (Groups 1 & 2) Interim CSR Phase 2/3 (United States)	BioNTech (Pfizer)	**Primary Objectives: Primary Safety (Safety Population):** To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age, and BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	**Cohort 2** BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 60 µg	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg 12 to 17 Years: N=107 18 to 55 Years: N=104 >55 Years: N=106 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg 18 to 55 Years: N=110 >55 Years N=102
		Primary Objective: Primary Immunogenicity (Evaluable Immunogenicity Population): Cohort 2: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg r 60 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age.	**Cohort 2** BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 60 µg **Study C4591031 Substudy E Expanded Cohort** BNT162b2	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg 12 to 17 Years: N=105 18 to 55 Years: N=95 >55 Years: N=102 BNT162b2 Bivalent

			Bivalent (WT/OMI BA.1) 30 µg BNT162b2 Bivalent (WT/OMI BA.1) 60 µg	(WT/OMI BA.4/BA.5) 60 µg 18 to 55 Years: N=102 >55 Years N=99 BNT162b2 Bivalent (WT/OMI BA.1) 30 µg 18 to 55 Years: N=100 >55 Years: N=100 BNT162b2 Bivalent (WT/OMI BA.1) 60 µg 18 to 55 Years: N=100 >55 Years N=100
		Primary Immunogenicity: Cohort 2/Group 4 + Cohort 3/ Group 2 combined: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to after BNT162b2 30 µg given as a second booster dose to BNT162b2- experienced participants >55 years of age. **Primary Immunogenicity:** Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age. **Secondary Objectives: Secondary Immunogenicity (Evaluable Immunogenicity Population):** Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority of the anti–reference-strain immune response after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg given as a second booster dose in BNT162b2- experienced participants >55 years of age. **Secondary Immunogenicity (Evaluable Immunogenicity Population):** Cohort 2/Group 2 + Cohort 3/Group 1 combined and	BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg **Study C4591031 Substudy E Expanded Cohort** Original BNT162b2 30 µg	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg 18 to 55 Years: N=297 >55 Years: N=286 BNT162b2 Original >55 Years: N=289

		Cohort 2/Group 4 + Cohort 3/Group 2 combined: To describe the immune response to BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg given as a second booster dose to BNT162b2- experienced participants 18 through 55 and >55 years of age.		

2.6.2.3.1. Study C4591048, substudy D

Substudy D is a Phase 3 open-label study to evaluate the safety, tolerability, and immunogenicity of a third or fourth dose with bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg in approximately 250 participants.

The protocol planned for enrolment of approximately 200 participants ≥5 to <12 years of age, who have received 2 or 3 prior doses of Original BNT162b2 10 µg, with their last dose 90 to 240 days prior to enrolment, that were offered a third or fourth dose of bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10-µg. This would include 100 participants who have completed 2 prior doses of original BNT162b2 10-µg and up to 100 participants who have completed 3 prior doses of original BNT162b2 10-µg.

Up to approximately 50 participants ≥5 to <12 years of age, who have completed 3 prior doses of original BNT162b2 at least 90 days prior to enrolment, were enrolled from Study C4591007 Phase 1 and offered a fourth dose of bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10-µg.

This report for Substudy D presents the following 1-month postdose data for approximately 100 participants ≥5 to <12 years of age from C4591048 Substudy D (Group 2) as of 25 NOV 2022 and approximately 100 participants of the same age from Study C4591007 (Phase 2/3) as of 27 MAY 2022:

- Immunogenicity data from C4591048 Substudy D (Group 2) participants who received a fourth dose (booster) with bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10-µg after receiving 3 prior doses of original BNT162b2 10-µg compared with C4591007 Phase 2/3 participants who received 3 doses of original BNT162b2 10 µg.

- **Immunogenicity Endpoints and Analysis Methods**

Primary Immunogenicity Objectives	Primary Immunogenicity Estimands	Primary Immunogenicity Endpoints
• To descriptively compare the anti–Omicron BA.4/BA.5 immune response between participants ≥5 to <12 years of age who received 3 prior doses of BNT162b2 10 µg and received bivalent BNT162b2 as a fourth dose in Group 2 and Study C4591007 Phase 2/3 participants ≥5 to <12 years of age who received 3 doses of BNT162b2 10 µg.	In participants complying with the key protocol criteria (evaluable participants): GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 Omicron BA.4/BA.5–neutralizing titers at 1 month after Dose 4 for participants who received 3 prior doses of BNT162b2 10 µg and a fourth dose of bivalent BNT162b2 to those at 1 month after Dose 3 for Study C4591007 Phase 2/3 participants who received 3 doses of BNT162b2 10 µg. The difference in percentage of participants with seroresponse to the Omicron BA.4/BA.5 strain between participants who received 3 prior doses of BNT162b2 10 µg and a fourth dose of bivalent BNT162b2 and Study C4591007 Phase 2/3 participants who received 3 doses of BNT162b2 10 µg at 1 month after Dose 3	• SARS-CoV-2 Omicron BA.4/BA.5–neutralizing titers

• **Secondary Immunogenicity:**	**Secondary Immunogenicity:**	• **Secondary Immunogenicity:**
• To describe the immune response elicited by bivalent BNT162b2 given as a fourth dose in participants ≥5 to <12 years of age.	In participants complying with the key protocol criteria (evaluable participants), for each strain-specific neutralizing titer: • GMTs at each time point • GMFR from before the study vaccination to each subsequent time point Percentages of participants with seroresponse at each time point following vaccination	• SARS-CoV-2 Omicron BA.4/BA.5–neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers

Descriptive immunogenicity analyses were performed to characterize Omicron BA.4/BA.5 and reference strain neutralization responses following a fourth dose with bivalent BNT162b2 (Original/Omi BA.4/BA.5) (C4591048 Substudy D Group 2 participants) or after 3 doses of BNT162b2 (C4591007 Phase 2/3 Participants) each at 10 µg. The validated SARS-CoV-2 neutralization assay was used to determine Omicron BA.4/BA.5- and reference strain-specific neutralizing titers.

GMTs and GMFRs with 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the tiers and fold rises, respectively, and the corresponding CIs (based on Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

GMR and associated 95% CIs were calculated by exponentiating the difference in LS means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model that includes the baseline neutralizing titer, postbaseline infection status, and vaccine group as covariates.

Unadjusted GMR was calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided CIs were obtained by calculating CIs using the Student t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

Seroresponse was defined as achieving a ≥4-fold rise from baseline (before the study vaccination [fourth dose If the baseline measurement was below the LLOQ, the postvaccination measure of ≥4 × LLOQ was considered seroresponse.

The adjusted difference in percentages of participants with seroresponse, and the associated 2-sided 95% CIs, were calculated using the Miettinen and Nurminen method stratified by baseline neutralizing titer category (<median, ≥median). The unadjusted difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs were calculated using the Miettinen and Nurminen method.

- **Immunogenicity Population**

A total of 115 participants ≥5 to <12 years of age were assigned to receive a fourth dose with the bivalent BNT162b2 (Original/Omi BA.4/BA.5) at 10 μg (***Table 9***).

Table 9.

Immunogenicity Populations – C4591048 Substudy D Group 2 and Study C4591007 Phase 2/3 Participants

	Vaccine Group (as Assigned/Randomized)	
	C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg	C4591007 BNT162b2 10 µg
	n[a] (%)	n[a] (%)
Assigned[b]	115 (100.0)	113 (100.0)
Dose 4 (C4591048)/Dose 3 (C4591007) all-available immunogenicity population	104 (90.4)	113 (100.0)
Excluded from Dose 4 (C4591048)/Dose 3 (C4591007) all-available immunogenicity population	11 (9.6)	0
Reason for exclusion		
Participant did not receive Dose 4 (C4591048)/Dose 3 (C4591007)	2 (1.7)	0
Did not have at least 1 valid and determinate immunogenicity result after Dose 4 (C4591048)/Dose 3 (C4591007)	9 (7.8)	0
Dose 4 (C4591048)/Dose 3 (C4591007) evaluable immunogenicity population	103 (89.6)	113 (100.0)
Participants without evidence of infection up to 1 month after Dose 4 (C4591048)/Dose 3 (C4591007)[c]	43 (37.4)	45 (39.8)
Excluded from Dose 4 (C4591048)/Dose 3 (C4591007) evaluable immunogenicity population	12 (10.4)	0
Reason for exclusion[d]		
Did not receive Dose 4 (C4591048)/Dose 3 (C4591007) vaccine as assigned/randomized	2 (1.7)	0
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 4 (C4591048)/Dose 3 (C4591007)	9 (7.8)	0
Had blood draw within the window but no valid and determinate immunogenicity result obtained in laboratory	1 (0.9)	0
No blood drawn at 1-Month post–Dose 4 (C4591048)/post–Dose 3 (C4591007)	8 (7.0)	0
Had other important protocol deviation	2 (1.7)	0

Abbreviations: N/A = not applicable; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations.
c. Participants with no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 4 (C4591048) or the 1-month post–Dose 3 (C4591007) blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 4 for C4591048 participants was defined as having a negative N-binding antibody (serum) result at the Dose 4 visit and 1-month post–Dose 4 visit; a negative NAAT (nasal swab) result at the Dose 4 visit, and any unscheduled visit up to the 1-month post–Dose 4 blood sample collection; and had no medical history of COVID-19.Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 for C4591007 participants was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–dose 3 visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 visits and any unscheduled visit up to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
d. Participants may have been excluded for more than 1 reason.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 02MAR2023 (10:03)
(Data cutoff date: C4591048 Substudy D[25NOV2022]/C4591007[27MAY2022])
Output File: ./nda2 ubped2/C4591048 D 1MPD 1007 Immuno/adva s008 immu pop p2 12

- **Demographics of Immunogenicity Population**

Demographic characteristics of participants with or without evidence of infection in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups are shown in ***Table 10***. A total of 57.3% of

participants in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group were baseline positive at the time of study vaccination (Dose 4). Median time since last dose of BNT162b2 before study vaccination (Dose 4) was 5.5 months in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group. In the BNT162b2 group, 58.4% of participants were baseline positive prior to Dose 3. Median time between Dose 2 and Dose 3 of BNT162b2 was 6.5 months in the BNT162b2 group.

Demographic characteristics for participants without evidence of infection up to 1 month after study vaccination in the evaluable immunogenicity population and the all-available immunogenicity population with or without evidence of infection were generally similar.

Table 10.

Demographic Characteristics – Participants With or Without Evidence of Infection – C4591048 Substudy D Group 2 and Study C4591007 Phase 2/3 Participants – Evaluable Immunogenicity Population

	Vaccine Group (as Assigned/Randomized)	
	C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg (N^a=103)	C4591007 BNT162b2 10 µg (N^a=113)
	n^b (%)	n^b (%)
Sex		
Male	49 (47.6)	63 (55.8)
Female	54 (52.4)	50 (44.2)
Race		
White	63 (61.2)	91 (80.5)
Black or African American	8 (7.8)	4 (3.5)
Asian	12 (11.7)	11 (9.7)
Native Hawaiian or other Pacific Islander	0	2 (1.8)
Multiracial	17 (16.5)	4 (3.5)
Not reported	3 (2.9)	1 (0.9)
Ethnicity		
Hispanic/Latino	23 (22.3)	16 (14.2)
Non-Hispanic/non-Latino	80 (77.7)	97 (85.8)
Age (years) at Dose 4 (C4591048)/Dose 3 (C4591007)		
Mean (SD)	8.6 (1.65)	8.6 (1.65)
Median	9.0	9.0
Min, max	(5, 11)	(5, 11)
Time (months[c]) from last prior BNT162b2 dose to Dose 4 (C4591048)/Dose 3 (C4591007)		
n	103	113
Mean (SD)	6.0 (1.45)	6.6 (0.31)
Median	5.5	6.5
Min, max	(3.5, 8.5)	(6.3, 7.6)
≥3 to <4 Months	7 (6.8)	0
≥4 to <5 Months	26 (25.2)	0
≥5 to <6 Months	22 (21.4)	0
≥6 to <7 Months	13 (12.6)	99 (87.6)
≥7 to <8 Months	23 (22.3)	14 (12.4)
≥8 to <9 Months	12 (11.7)	0
Time (days) from last prior BNT162b2 dose to Dose 4 (C4591048)/Dose 3 (C4591007)		

n	103	113
Mean (SD)	168.5 (40.51)	185.1 (8.60)
Median	154.0	183.0
Min, max	(98, 239)	(175, 212)
90-240 Days	103 (100.0)	113 (100.0)
Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 status		
Positive[d]	59 (57.3)	66 (58.4)
Negative[e]	44 (42.7)	47 (41.6)
Comorbidities[f]		
Yes	28 (27.2)	33 (29.2)
No	75 (72.8)	80 (70.8)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Month was calculated as 28 days.
d. For C4591048 Substudy D Group 2: positive N-binding antibody result at the Dose 4 visit, positive NAAT result at the Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visit, positive NAAT result at the Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to the Dose 3 visit, or medical history of COVID-19.
e. For C4591048 Substudy D Group 2: negative N-binding antibody result at the Dose 4 visit, negative NAAT result at the Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at the Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to the Dose 3 visit, and no medical history of COVID-19.
f. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR Morb Mortal Wkly Rep. 2020;69(32):1081-8 and/or obesity (BMI ≥95th percentile). Comorbidities were assessed at the first study visit for both studies.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 02MAR2023 (09:47)
(Data cutoff date: C4591048 Substudy D[25NOV2022]/C4591007[27MAY2022])
Output File: ./nda2_ubped2/C4591048_D_1MPD_1007_Immuno/adsl_s005_demo_p2_12_evl

- **Immunogenicity results**

GMR

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population with or without evidence of prior infection up to 1 month after study vaccination, model-based GMR of Omicron BA.4/BA.5-neutralizing titers for the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group to the BNT162b2 group was 1.12 (2-sided 95% CI: 0.92, 1.37) (***Table 11***). Unadjusted GMR was 1.57 (2-sided 95% CI: 1.18, 2.09).

Table 11.

Model-Based Geometric Mean Ratio – C4591048 Substudy D Group 2 (1 Month After Dose 4) to C4591007 Phase 2/3 Participants (1 Month After Dose 3) – With or Without Evidence of Infection – Evaluable Immunogenicity Population

	Vaccine Group (as Assigned/Randomized)				
	C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg		C4591007 BNT162b2 10 µg		Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg/BNT162b2 10 µg
Assay	n[a]	GMT[b] (95% CI[b])	n[a]	GMT[b] (95% CI[b])	GMR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	101	1836.1 (1593.8, 2115.2)	112	1632.5 (1427.5, 1867.0)	1.12 (0.92, 1.37)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 140 days prior to enrollment.
a. n = Number of participants with valid and determinate assay results for the specified assay at both the given dose and the given sampling time point.
b. GMTs and 2-sided CIs were calculated by exponentiating the LSMeans 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.
c. GMRs and 2-sided CIs were calculated by exponentiating the difference of LSMeans for the assay and the corresponding CIs based on the same regression model as stated above.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 02MAR2023 (09:44)
Data cutoff date: C4591048 Substudy D[25NOV2022]/C4591007[27MAY2022])
Output File: ./nda2_ubped2/C4591048_D_1MPD_1007_Immuno/adva_s004_gmrb_p2_evl

Seroresponse

Omicron BA.4/BA.4 Neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity participants with or without evidence of prior infection up to 1-month postdose, 53.5% of participants in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group achieved seroresponse to Omicron BA.4/BA.5. The adjusted difference in percentages of participants with seroresponse between the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group and the BNT162b2 group was 8.76% (95% CI: -2.47, 19.99) (***Table 11***). Unadjusted difference in seroresponse rates was 0.79% (95% CI: -12.57, 14.10).

Table 12.

Adjusted Difference in Percentages of Participants With Seroresponse Between C4591048 Substudy D Group 2 (1 Month After Dose 4) and C4591007 Phase 2/3 Participants (1 Month After Dose 3) – With or Without Evidence of Infection – Evaluable Immunogenicity Population

	Vaccine Group (as Assigned/Randomized)							
	C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg			C4591007 BNT162b2 10 µg			Difference	
Assay	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	%[d]	(95% CI[e])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	101	54 (53.5)	(43.3, 63.5)	112	59 (52.7)	(43.0, 62.2)	8.76	(-2.47, 19.99)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 4 for C4591048 Substudy D Group 2 and before Dose 3 for C4591007). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. N = number of participants with valid and determinate assay results for the specified assay both before Dose 4 (C4591048)/Dose 3 (C4591007) and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Adjusted difference in proportions based on the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median), expressed as a percentage (bivalent BNT162b2 [original/Omi BA.4/BA.5] 10 µg - BNT162b2 10 µg). The median of baseline neutralizing titers was calculated based on the pooled data in 2 comparator groups.
e. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions stratified by baseline neutralizing titer category (< median, ≥ median), expressed as a percentage.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 02MAR2023 (09:44)
(Data cutoff date: C4591048 Substudy D[25NOV2022]/C4591007[27MAY2022])
Output File: ./nda2_ubped2/C4591048_D_1MPD_1007_Immuno/adva_s003_diff_sero_p2_evl

GMT

Omicron BA.4/BA.5 neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population with or without evidence of prior infection, for both vaccine groups, GMTs against the Omicron BA.4/BA.5 variant were higher at predose and at 1-month postdose in participants who were baseline positive compared with those who were baseline negative (*Table 13*).

Within both baseline positive and baseline negative groups, BA.4/BA.5-neutralizing GMTs were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with that in the BNT162b2 group at prevaccination. For baseline positive participants, BA.4/BA.5- neutralizing GMTs at 1month postdose were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group. For baseline negative participants, the observed GMTs at 1-month postdose were generally similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups, despite lower prevaccination values in the BNT162b2 group. The results are not as good as observed in previous studies for the bivalent group relative to the original vaccine group, especially for baseline negative participants. Lack of randomization (which results in substantial prevaccination titer differences between groups and potential imbalance in some participants characteristics) makes it very difficult to interpret the results.

GMTs across both sexes were similar within both vaccine groups.

Table 13

Geometric Mean Titers, by Subgroup – C4591048 Substudy D Group 2 (at Dose 4 and 1 Month After Dose 4) and C4591007 Phase 2/3 Participants (at Dose 3 and 1 Month After Dose 3) – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

			Vaccine Group (as Assigned/Randomized)			
			C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg		C4591007 BNT162b2 10 µg	
Assay	Subgroup	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	Overall	Prevax	102	488.3 (361.9, 658.8)	112	248.3 (187.2, 329.5)
		1 Month	102	2189.9 (1742.8, 2751.7)	113	1393.6 (1175.8, 1651.7)
	Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status[d]					
	Positive	Prevax	58	1069.2 (782.4, 1461.1)	65	695.0 (538.4, 897.3)
		1 Month	58	3465.6 (2682.8, 4476.7)	66	1893.9 (1547.6, 2317.7)
	Negative	Prevax	44	173.8 (117.3, 257.4)	47	59.8 (49.0, 73.1)
		1 Month	44	1195.8 (850.2, 1681.9)	47	905.8 (703.0, 1167.2)
	Sex					
	Male	Prevax	49	608.6 (394.7, 938.4)	62	242.0 (164.1, 356.8)
		1 Month	48	2442.8 (1749.9, 3410.2)	63	1506.8 (1203.1, 1887.2)
	Female	Prevax	53	398.3 (261.5, 606.6)	50	256.5 (167.3, 393.2)
		1 Month	54	1987.2 (1441.3, 2739.8)	50	1263.0 (968.7, 1646.6)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	Overall	Prevax	102	2904.0 (2372.6, 3554.5)	113	1323.1 (1055.7, 1658.2)
		1 Month	102	8245.9 (7108.9, 9564.9)	113	7235.1 (6331.5, 8267.8)
	Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status[d]					
	Positive	Prevax	58	4198.4 (3342.9, 5272.8)	66	2672.7 (2122.4, 3365.6)
		1 Month	58	9228.4 (7707.0, 11050)	66	7632.5 (6471.6, 9001.5)
	Negative	Prevax	44	1786.4 (1305.0, 2445.5)	47	492.9 (390.9, 621.6)
		1 Month	44	7108.8 (5534.0, 9131.8)	47	6711.9 (5345.4, 8427.7)
	Sex					
	Male	Prevax	49	3369.3 (2480.9, 4575.8)	63	1337.6 (1001.9, 1785.7)
		1 Month	48	8728.6 (6921.6, 11007)	63	7912.0 (6652.6, 9409.9)
	Female	Prevax	53	2531.3 (1929.9, 3320.0)	50	1305.1 (902.3, 1887.7)
		1 Month	54	7839.4 (6443.6, 9537.5)	50	6464.1 (5237.5, 7977.9)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
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 titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive = For C4591048 Substudy D Group 2: positive N-binding antibody result at the Dose 4 visit, positive NAAT result at the Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visit, positive NAAT result at the Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to the Dose 3 visit, or medical history of COVID-19.
Negative = For C4591048 Substudy D Group 2: negative N-binding antibody result at the Dose 4 visit, negative NAAT result at the Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at the Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to the Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 02MAR2023 (09:44)
(Data cutoff date: C4591048 Substudy D[25NOV2022]/C4591007[27MAY2022])
Output File: ./nda2_ubped2/C4591048_D_1MPD_1007_Immuno/adva_s001_gmt_p2_evl

Reference Strain Neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population with or without evidence of prior infection, for both vaccine groups, the observed reference strain GMTs were higher at predose and generally similar or higher at 1 month postdose in participants who were baseline positive compared with those who were baseline negative (Table 16).

Within both baseline positive and baseline negative groups, the observed reference strain- neutralizing GMTs were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) compared with that in the BNT162b2 group at prevaccination. For baseline positive participants, at 1-month postdose, the observed reference strain-neutralizing GMTs were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group. For baseline negative participants, reference strain-specific neutralizing GMTs were generally similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups.

GMTs across both sexes were similar within both vaccine groups.

Participants Without Evidence of Infection

In the evaluable immunogenicity population without evidence of prior infection, the observed reference strain-neutralizing GMTs at pre-vaccination were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group.

At 1-month postdose, the observed GMTs were generally similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with those in the BNT162b2 group

GMFR

Omicron BA.4/BA.5 neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity populations with or without evidence of prior infection, for both vaccine groups, GMFRs of Omicron BA.4/BA.5 at 1-month post dose were higher in participants who were baseline negative compared with those who were baseline positive (bivalent BNT162b2 [Original/Omi BA.4/BA.5]: 6.9 vs 3.3, BNT162b2: 15.1 vs 2.7) (*Table 14*).

For baseline positive participants, GMFRs at 1-month postdose were similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups. For baseline negative participants, GMFRs were lower in the

bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group, which may relate to the higher prevaccination titers in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group.

GMFRs across both sexes were similar within both vaccine groups.

Participants Without Evidence of Infection

In the evaluable immunogenicity population without evidence of infection, GMFRs for Omicron BA.4/BA.5 at 1-month postdose were lower in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (6.9; 2-sided 95% CI: 5.4, 8.8) compared with the BNT162b2 group (15.0; 2-sided 95% CI: 12.2, 18.4).

Reference Strain Neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity populations with or without evidence of infection, for both vaccine groups, GMFRs of reference strain at 1-month postdose were higher for participants who were baseline negative compared with those who were baseline positive (bivalent BNT162b2 [Original/Omi BA.4/BA.5]: 4.0 vs 2.2, BNT162b2: 13.6 vs 2.9) (***Table 14***).

For baseline positive participants, GMFRs at 1-month postdose were similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups. For baseline negative participants, GMFRs were lower in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group, which may relate to the higher prevaccination titers in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group.

GMFRs across both sexes were similar within both vaccine groups.

Participants Without Evidence of Infection

In the evaluable immunogenicity population without evidence of infection, reference strain GMFRs from prevaccination to 1-month postdose were lower in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (4.0; 2-sided 95% CI: 3.3, 4.8) compared with the BNT162b2 group (13.1; 2-sided 95% CI: 10.5, 16.4).

Table 14

Geometric Mean Fold Rises by Subgroup – C4591048 Substudy D Group 2 (From Dose 4 to 1 Month After Dose 4) and C4591007 Phase 2/3 Participants (From Dose 3 to 1 Month After Dose 3) – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

Assay	Subgroup	Sampling Time Point[a]	BNT162b2 (Original/Omi BA.4/BA.5) 10 µg		p (as mized) C4591007 T162b2 10 µg	
			n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	Overall	1 Month	101	4.5 (3.8, 5.4)	112	5.6 (4.5, 6.9)
	Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status[d]					
	Positive	1 Month	57	3.3 (2.6, 4.1)	65	2.7 (2.2, 3.3)
	Negative	1 Month	44	6.9 (5.4, 8.7)	47	15.1 (12.1, 18.9)
	Sex					
	Male	1 Month	48	4.0 (3.2, 5.1)	62	6.2 (4.6, 8.4)
	Female	1 Month	53	5.0 (3.8, 6.5)	50	4.9 (3.6, 6.8)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	Overall	1 Month	101	2.8 (2.5, 3.3)	113	5.5 (4.5, 6.7)
	Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status[d]					
	Positive	1 Month	57	2.2 (1.8, 2.6)	66	2.9 (2.4, 3.4)
	Negative	1 Month	44	4.0 (3.3, 4.7)	47	13.6 (10.9, 17.1)
	Sex					
	Male	1 Month	48	2.6 (2.1, 3.2)	63	5.9 (4.5, 7.8)
	Female	1 Month	53	3.1 (2.5, 3.7)	50	5.0 (3.7, 6.6)

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
a. Protocol-specified timing for blood sample collection.
b. n = number of participants with valid and determinate assay results for the specified assay both before Dose 4 (C4591048)/Dose 3 (C4591007) and at the given dose/sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
d. Positive = For C4591048 Substudy D Group 2: positive N-binding antibody result at the Dose 4 visit, positive NAAT result at the Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visit, positive NAAT result at the Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to the Dose 3 visit, or medical history of COVID-19.
Negative = For C4591048 Substudy D Group 2: negative N-binding antibody result at the Dose 4 visit, negative NAAT result at the Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at the Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to the Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 02MAR2023 (09:44)
(Data cutoff date: C4591048 Substudy D[25NOV2022]/C4591007[27MAY2022])
Output File: ./nda2_ubped2/C4591048_D_1MPD_1007_Immuno/advas_s001_gmfr_p2_evl

Seroresponse

Omicron BA.4/BA.5 neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population with or without evidence of prior infection, seroresponse rates at 1-month postdose were generally higher for participants who were baseline negative compared with those who were baseline positive (bivalent BNT162b2 [Original/Omi BA.4/BA.5]: 75.0% vs. 36.8%, BNT162b2: 89.4% vs 26.2%) (***Table 15***).

For baseline positive groups, seroresponse rates at 1-month postdose were slightly higher in participants in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) compared with the BNT162b2 group. For baseline negative groups, seroresponse rates at 1-month postdose were slightly lower in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) compared with the BNT162b2 group (***Table 15***).

Seroresponse rates across both sexes were generally similar within both vaccine groups.

Participants Without Evidence of Infection

In the evaluable immunogenicity population without evidence of prior infection, the proportion of participants who achieved seroresponse at 1-month postdose were generally lower in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (74.4%) compared with the BNT162b2 group (91.1%).

Reference Strain Neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population with or without evidence of prior infection, seroresponse rates at 1-month postdose were higher for participants who were baseline negative compared to those who were baseline positive (bivalent BNT162b2 [Original/Omi BA.4/BA.5]: 47.7% vs. 17.5%, BNT162b2: 95.7% vs 25.8%) (***Table 15***).

For baseline positive participants, seroresponse rates at 1-month postdose were generally similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups. For baseline negative participants, seroresponse rates were lower in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group, which relate to the higher prevaccination titers in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (***Table 15***).

Seroresponse rates across both sexes were generally similar within both vaccine groups.

Participants Without Evidence of Infection

In the evaluable immunogenicity population without evidence of prior infection, the proportion of participants who achieved seroresponse at 1-month postdose were lower in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (48.8%) compared with the BNT162b2 group (95.6%).

Table 15.

Number (%) of Participants With Seroresponse, by Subgroup – C4591048 Substudy D Group 2 (at 1 Month After Dose 4) and C4591007 Phase 2/3 Participants (1 Month After Dose 3) – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

			Vaccine Group (as Assigned/Randomized)			
			C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg		C4591007 BNT162b2 10 µg	
Assay	Subgroup	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	Overall	1 Month	101	54 (53.5) (43.3, 63.5)	112	59 (52.7) (43.0, 62.2)
	Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status[e]					
	Positive	1 Month	57	21 (36.8) (24.4, 50.7)	65	17 (26.2) (16.0, 38.5)
	Negative	1 Month	44	33 (75.0) (59.7, 86.8)	47	42 (89.4) (76.9, 96.5)
	Sex					
	Male	1 Month	48	23 (47.9) (33.3, 62.8)	62	35 (56.5) (43.3, 69.0)
	Female	1 Month	53	31 (58.5) (44.1, 71.9)	50	24 (48.0) (33.7, 62.6)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	Overall	1 Month	101	31 (30.7) (21.9, 40.7)	113	62 (54.9) (45.2, 64.2)
	Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status[e]					
	Positive	1 Month	57	10 (17.5) (8.7, 29.9)	66	17 (25.8) (15.8, 38.0)
	Negative	1 Month	44	21 (47.7) (32.5, 63.3)	47	45 (95.7) (85.5, 99.5)
	Sex					
	Male	1 Month	48	13 (27.1) (15.3, 41.8)	63	36 (57.1) (44.0, 69.5)
	Female	1 Month	53	18 (34.0) (21.5, 48.3)	50	26 (52.0) (37.4, 66.3)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 4 for C4591048 Substudy D Group 2 and before Dose 3 for C4591007). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥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 both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Positive = For C4591048 Substudy D Group 2: positive N-binding antibody result at the Dose 4 visit, positive NAAT result at the Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visit, positive NAAT result at the Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to the Dose 3 visit, or medical history of COVID-19.
Negative = For C4591048 Substudy D Group 2: negative N-binding antibody result at the Dose 4 visit, negative NAAT result at the Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at the Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to the Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 02MAR2023 (09:44)
(Data cutoff date: C4591048 Substudy D[25NOV2022]/C4591007[27MAY2022])
Output File: ./nda2 ubped2/C4591048 D 1MPD 1007 Immuno/adva s003 fr4 p2 evl

MAH discussion of immunogenicity results for C4591048 Substudy D Group 2 (5y-<12 yoa)

At 1-month postdose, a fourth dose with bivalent BNT162b2 (Original/Omi BA.4/BA.5) at 10 µg in participants ⩾5 years to <12 years of age in the C4591048 Substudy D Group 2 who received 3 prior doses of original BNT162b2 at 10 µg indicated a robust immune response against Omicron BA.4/BA.5. The immune response elicited by bivalent BNT162b2 (Original/Omi BA.4/BA.5) were generally similar for Omicron BA.4/BA.5- and reference strain-specific neutralizing titers and percentage of participants with seroresponse to Omicron BA.4/BA.5 compared with C4591007 Phase 2/3 participants of the same age who received 3 doses of original BNT162b2.

The magnitude of the Omicron BA.4/BA.5 immune response after Dose 3 of BNT162b2 is unexpected and may be related to natural exposure and dose interval. As this analysis did not compare 2 contemporaneous randomized groups, there may have been an imbalance between the 2 groups in some measurable or nonmeasurable factors, such as those described below. This imbalance may have contributed to the unexpected results. Participants in C4591007 Phase 2/3 received the third dose in March-April 2022, shortly after the Omicron BA.1 wave.

Whilst not reflected in the N-binding antibody responses, this may have resulted in a significant level of natural exposure to Omicron BA.1; thereby, potentially augmenting the response to Dose 3 of BNT162b2. The prevaccination GMTs also may have influenced the magnitude of the response to the booster dose (either Dose 3 or Dose 4), as they were higher in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group than in the comparator group. In addition, this difference may be due to the shorter interval between Dose 3 and Dose 4 in the BNT162b2 (Original/Omi BA.4/BA.5) group (5.5 months, range 3.5-8.5 months) compared with the dose interval between Dose 2 and Dose 3 in the BNT162b2 group (6.5 months, range 6.3-7.6 months). However, it may be more likely due to participants in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group receiving the fourth dose in September- October 2022. Hence, these participants had a 6-month longer period of potential exposure to SARS-CoV-2 during the waves of multiple Omicron sublineages in 2022. The higher prevaccination GMTs were reflected in the lower GMFRs and seroresponse rates in participants who received a fourth dose with the bivalent BNT162b2 (Original/Omi BA.4/BA.5) compared with participants in C4591007 Phase 2/3 who received 3 doses of original BNT162b2.

2.6.2.3.2. Study C4591044

Study C4591044 is a randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of new bivalent vaccines. The study participants are divided into cohorts, which may be studied in a staggered or parallel manner. Cohorts 2 and 3 in the study consist of participants ≥12 years of age who received 3 doses of BNT162b2, each at 30 µg, prior to receiving a booster (fourth dose) with BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at the 30- or 60-µg dose level. The groups within each cohort and the dose level of the study vaccine are defined in ***Table 16***. The MAH has provided 1-month post dose (four) immunogenicity data for the participants.

Table 16.

Study C4591044 Cohorts 2 and 3

Cohort Number	Group Number	Age (Years)	Booster (Fourth Dose) With BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (µg)
2	1	12 to 17	30
	2	18 to 55	30
	3	18 to 55	60
	4	>55	30
	5	>55	60
3	1	18 to 55	30
	2	>55	30

- **Immunogenicity Endpoints and Analysis Methods**

Objectives, Estimands and Endpoints

Objectives	Estimands	Endpoints	Reference
Primary Immunogenicity			
Cohort 2/Group 4 + Cohort 3/ Group 2 combined: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to after BNT162b2 30 µg[c] given as a second booster dose to BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) to 1 month after BNT162b2, given as a second booster dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers	• Data are reported in this CSR

Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers	• Data are reported in this CSR
Cohort 2: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg[e] or 60 µg[e] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55[e], and >55[e] years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at **each time point** for each strain-specific neutralizing titer • GMFR from before the study vaccination to **each subsequent time point** for each strain-specific neutralizing titer • Percentages of participants with seroresponse at **each time point** following vaccination for each strain- specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers	• Immunogenicity data before and at 1 month after study vaccination are reported in this CSR
Objectives	**Estimands**	**Endpoints**	**Reference**
Secondary Immunogenicity			

Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority of the anti–reference-strain immune response after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[c] given as a second booster dose in BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the reference-strain–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 reference- strain[c]–neutralizing titers	• Data are reported in this CSR
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To describe the immune response to BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[c] given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at **each time point** for each strain-specific neutralizing titer • GMFR from before the study vaccination to **each subsequent time point** for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at **each time point** following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference- strain[c]–neutralizing titers	• Immunogenicity data before and 1 month after study vaccination are reported in this CSR

a. SAEs are presented from vaccination through 1 month after vaccination in this interim CSR.

b. Seroresponse was defined as achieving a ≥4-fold rise from the baseline (before the study vaccination) at each timepoint after vaccination. If the baseline measurement was below the LLOQ, the postvaccination measure of ≥4 × LLOQ was considered seroresponse.

c. Reference strain was also referred to as the wild type or ancestral strain (Wuhan-Hu-1; USA-WA1/2020).

d. The participants >55 years of age from C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be used as comparator group for this objective.

e. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) and dose group (30 µg, 60 µg) from C4591031 Substudy E expanded cohort who received BNT162b2 Bivalent (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be selected for this objective. The subset selected from C4591031 Substudy E will include similar percentage of participants with baseline positive SARS-CoV-2 infection status as the groups in Cohort 2 of this study, whenever feasible.

f. If the COVID-19 illness visit was conducted as an in-person visit, a blood sample was taken for this assessment. No blood samples were obtained for remote (telehealth) COVID-19 illness visits.

- **Immunogenicity Population**

This part of the immunogenicity analysis included approximately 100 randomized participants per vaccine group (***Table 17***).

Table 17. Immunogenicity Populations – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort

	Vaccine Group (as Randomized)								
	C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)					C4591031 BNT162b2 Bivalent (WT/OMI BA.1)			
	12-17 Years	18-55 Years		>55 Years		18-55 Years		>55 Years	
	30 µg n[a] (%)	30 µg n[a] (%)	60 µg n[a] (%)	30 µg n[a] (%)	60 µg n[a] (%)	30 µg n[a] (%)	60 µg n[a] (%)	30 µg n[a] (%)	60 µg n[a] (%)
Randomized[b]	108 (100.0)	104 (100.0)	110 (100.0)	106 (100.0)	102 (100.0)	100 (100.0)	100 (100.0)	100 (100.0)	100 (100.0)
All-available immunogenicity population	107 (99.1)	97 (93.3)	105 (95.5)	105 (99.1)	101 (99.0)	100 (100.0)	100 (100.0)	100 (100.0)	100 (100.0)
Excluded from all-available immunogenicity population	1 (0.9)	7 (6.7)	5 (4.5)	1 (0.9)	1 (1.0)	0	0	0	0
Reason for exclusion[c]									
Participant did not receive study intervention	0	1 (1.0)	0	0	0	0	0	0	0
Did not have at least 1 valid and determinate immunogenicity result after study vaccination	0	7 (6.7)	5 (4.5)	1 (0.9)	1 (1.0)	0	0	0	0
Did not provide informed consent	1 (0.9)	0	0	0	0	0	0	0	0
Evaluable immunogenicity population	105 (97.2)	95 (91.3)	102 (92.7)	102 (96.2)	99 (97.1)	100 (100.0)	100 (100.0)	100 (100.0)	100 (100.0)
Participants without evidence of infection up to 1 month after study vaccination[d]	25 (23.1)	32 (30.8)	23 (20.9)	40 (37.7)	31 (30.4)	67 (67.0)	30 (30.0)	64 (64.0)	65 (65.0)
Excluded from evaluable immunogenicity population	3 (2.8)	9 (8.7)	8 (7.3)	4 (3.8)	3 (2.9)	0	0	0	0
Reason for exclusion[c]									
Did not meet eligibility and randomization criteria	0	5 (4.8)	3 (2.7)	0	0	0	0	0	0
Participant did not receive study intervention as randomized	0	1 (1.0)	0	0	0	0	0	0	0
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after study vaccination	2 (1.9)	9 (8.7)	6 (5.5)	4 (3.8)	3 (2.9)	0	0	0	0
Had important protocol deviation	1 (0.9)	5 (4.8)	4 (3.6)	0	0	0	0	0	0
Did not provide informed consent	1 (0.9)	0	0	0	0	0	0	0	0

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

Note: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.
a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations.
c. Participants may have been excluded for more than 1 reason.
d. Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7- day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 10JAN2023 (20:14) (Data cutoff date : C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adsl_s009_immpop_1m_c2f

- **Demographic**

Demographic characteristics for participants in Cohort 2 with or without evidence of infection up to 1 month after study vaccination in the evaluable immunogenicity population are presented in ***Table 18***.

Demographic characteristics for participants in the evaluable immunogenicity population with or without evidence of infection up to 1 month after study vaccination were similar to the safety population.

Demographic characteristics for participants without evidence of infection up to 1 month after study vaccination in the evaluable immunogenicity population and for participants with or without evidence of infection up to 1 month after study vaccination in the all-available immunogenicity population were generally similar to those in ***Table 18***.

Table 18. Demographic Characteristics – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)								
	C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)					C4591031 BNT162b2 Bivalent (WT/OMI BA.1)			
	12-17 Years	18-55 Years		>55 Years		18-55 Years		>55 Years	
	30 µg (N[a]=105) n[b] (%)	30 µg (N[a]=95) n[b] (%)	60 µg (N[a]=102) n[b] (%)	30 µg (N[a]=102) n[b] (%)	60 µg (N[a]=99) n[b] (%)	30 µg (N[a]=100) n[b] (%)	60 µg (N[a]=100) n[b] (%)	30 µg (N[a]=100) n[b] (%)	60 µg (N[a]=100) n[b] (%)
Sex									
Male	58 (55.2)	40 (42.1)	41 (40.2)	62 (60.8)	45 (45.5)	51 (51.0)	58 (58.0)	57 (57.0)	53 (53.0)
Female	47 (44.8)	55 (57.9)	61 (59.8)	40 (39.2)	54 (54.5)	49 (49.0)	42 (42.0)	43 (43.0)	47 (47.0)
Race									
White	89 (84.8)	75 (78.9)	83 (81.4)	80 (78.4)	89 (89.9)	77 (77.0)	86 (86.0)	89 (89.0)	83 (83.0)
Black or African American	9 (8.6)	9 (9.5)	11 (10.8)	16 (15.7)	8 (8.1)	7 (7.0)	7 (7.0)	7 (7.0)	11 (11.0)
American Indian or Alaska Native	0	0	0	1 (1.0)	0	0	0	0	0

Asian	3 (2.9)	9 (9.5)	8 (7.8)	3 (2.9)	2 (2.0)	14 (14.0)	4 (4.0)	4 (4.0)	5 (5.0)
Native Hawaiian or other Pacific Islander	0	0	0	1 (1.0)	0	2 (2.0)	1 (1.0)	0	0
Multiracial	3 (2.9)	2 (2.1)	0	1 (1.0)	0	0	2 (2.0)	0	1 (1.0)
Not reported	1 (1.0)	0	0	0	0	0	0	0	0
Age at vaccination (years)									
Median	15.0	40.0	41.0	65.0	63.0	42.0	39.5	66.0	67.0
Min, max	(12, 17)	(19, 55)	(18, 55)	(56, 79)	(56, 85)	(22, 55)	(18, 55)	(56, 85)	(56, 86)
Baseline SARS-CoV-2 status									
Positive[c]	79 (75.2)	62 (65.3)	75 (73.5)	62 (60.8)	67 (67.7)	33 (33.0)	70 (70.0)	36 (36.0)	35 (35.0)
Negative[d]	26 (24.8)	33 (34.7)	27 (26.5)	40 (39.2)	32 (32.3)	67 (67.0)	30 (30.0)	64 (64.0)	65 (65.0)
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (months[e])									
n	105	95	102	102	99	100	100	100	100
Median	8.4	10.9	10.8	10.9	10.9	8.6	8.5	6.3	6.3
Min, max	(5.6, 12.0)	(5.5, 12.8)	(6.6, 13.0)	(5.5, 12.9)	(6.6, 13.0)	(5.6, 13.0)	(5.4, 12.3)	(4.7, 11.5)	(5.4, 11.1)
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (days)									
n	105	95	102	102	99	100	100	100	100
Median	234.0	305.0	302.0	306.0	306.0	239.5	239.0	175.5	175.0
Min, max	(157, 335)	(155, 357)	(184, 364)	(153, 362)	(184, 363)	(158, 365)	(151, 343)	(131, 322)	(150, 312)
Body mass index (BMI)									
Number of participants ≥16 years of age[f]	44	95	102	102	99	100	100	100	100
Underweight (<18.5 kg/m^2)	5 (11.4)	1 (1.1)	6 (5.9)	3 (2.9)	1 (1.0)	1 (1.0)	2 (2.0)	0	0
Normal weight (≥18.5-24.9 kg/m^2)	28 (63.6)	38 (40.0)	23 (22.5)	27 (26.5)	22 (22.2)	20 (20.0)	27 (27.0)	22 (22.0)	23 (23.0)
Overweight (≥25.0-29.9 kg/m^2)	8 (18.2)	32 (33.7)	31 (30.4)	33 (32.4)	41 (41.4)	31 (31.0)	30 (30.0)	42 (42.0)	41 (41.0)
Obese (≥30.0 kg/m^2)	3 (6.8)	24 (25.3)	42 (41.2)	39 (38.2)	35 (35.4)	48 (48.0)	41 (41.0)	36 (36.0)	36 (36.0)

- **Immunogenicity results**

GMT

Analysis of immunogenicity data at 1 month after study vaccination in the evaluable immunogenicity population with or without evidence of infection for BNT162b2- experienced participants showed that BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 µg and 60 µg dose elicited robust immune response against Omicron BA.4/BA.5 in all age groups and the response was higher than the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups.

Omicron BA.4/BA.5 GMTs at prevaccination and 1 month after study vaccination were higher in participants who were baseline positive compared with those were baseline negative in all age and vaccine groups.

Within baseline positive or baseline negative groups, Omicron BA.4/BA.5 GMTs were:

- Higher in participants 12 through 17 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared with other age and vaccine groups at both prevaccination and 1 month after vaccination.
- Larger increase from prevaccination in participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg and 60-µg groups compared with participants in the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups. The differences between BNT162b2 Bivalent (WT/OMI BA.4/BA.5) groups and BNT162b2 Bivalent (WT/OMI BA.1) were more substantial in the baseline negative groups.
- Generally similar in participants 18 through 55 and >55 years of age who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either dose.
- Higher overall in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60-µg group compared with that in the 30-µg group.
- Generally similar across both sexes within each age and dose group.

Table 19

14.20. Geometric Mean Titers, by Subgroup – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

				Vaccine Group (as Randomized)			
				C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		C4591031 BNT162b2 Bivalent (WT/OMI BA.1)	
Assay	Dosage/Age Group	Subgroup	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	30 µg/12-17 years	All	Prevax	104	1105.8 (835.1, 1464.3)	N/A	N/A
			1 Month	105	8212.8 (6807.3, 9908.7)	N/A	N/A
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	78	1791.1 (1379.6, 2325.3)	N/A	N/A
			1 Month	79	9892.5 (8114.6, 12059.8)	N/A	N/A
		Negative[e]	Prevax	26	260.2 (157.1, 430.9)	N/A	N/A
			1 Month	26	4666.1 (3096.1, 7032.2)	N/A	N/A
	30 µg/18-55 years	All	Prevax	95	338.3 (238.1, 480.7)	100	151.5 (113.4, 202.3)
			1 Month	95	2839.0 (2150.0, 3748.8)	100	1072.0 (816.1, 1408.1)
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	62	900.3 (661.5, 1225.2)	33	558.4 (338.6, 920.9)
			1 Month	62	4678.4 (3438.9, 6364.6)	33	2271.4 (1346.7, 3831.2)
		Negative[e]	Prevax	33	53.8 (41.1, 70.5)	67	79.7 (62.7, 101.1)
			1 Month	33	1110.7 (743.9, 1658.4)	67	740.6 (557.2, 984.2)

	30 µg/>55 years	All	Prevax	101	301.9 (215.6, 422.8)	99	225.4 (164.1, 309.6)
			1 Month	102	3019.8 (2327.5, 3918.0)	100	943.4 (733.4, 1213.6)
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	61	745.8 (516.5, 1076.9)	36	948.9 (576.4, 1562.1)
			1 Month	62	4386.5 (3263.2, 5896.4)	36	2334.3 (1524.5, 3574.3)
		Negative[e]	Prevax	40	76.0 (54.7, 105.7)	63	99.1 (78.1, 125.8)
			1 Month	40	1693.1 (1094.0, 2620.1)	64	566.7 (446.2, 719.9)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	30 µg/12-17 years	All	Prevax	105	6863.3 (5587.8, 8430.1)	N/A	N/A
			1 Month	105	23641.3 (20473.1, 27299.8)	N/A	N/A
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	79	8685.4 (7062.7, 10680.9)	N/A	N/A
			1 Month	79	25991.8 (22377.5, 30189.8)	N/A	N/A
		Negative[e]	Prevax	26	3356.2 (2106.9, 5346.2)	N/A	N/A
			1 Month	26	17725.2 (12376.4, 25385.7)	N/A	N/A
	30 µg/18-55 years	All	Prevax	95	2349.0 (1693.4, 3258.4)	100	1338.4 (1056.9, 1695.1)
			1 Month	95	11919.3 (9839.1, 14439.3)	99	6913.9 (5690.4, 8400.5)
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	62	5615.4 (4406.4, 7156.1)	33	3183.8 (2185.4, 4638.2)
			1 Month	62	16214.4 (13340.3, 19707.6)	32	10119.7 (7341.3, 13949.6)
		Negative[e]	Prevax	33	456.8 (291.5, 716.0)	67	873.5 (682.8, 1117.3)
			1 Month	33	6685.8 (4731.8, 9446.9)	67	5763.8 (4550.1, 7301.1)

30 µg/>55 years	All	Prevax	101	2643.1 (1990.8, 3509.1)	100	1985.7 (1510.1, 2611.0)
		1 Month	102	12103.8 (9992.0, 14662.0)	100	7128.6 (5954.4, 8534.3)
	Baseline SARS-CoV-2 status					
	Positive[d]	Prevax	61	5428.8 (4112.6, 7166.3)	36	6390.0 (4353.9, 9378.3)
		1 Month	62	15336.7 (12079.9, 19471.6)	36	12362.0 (9000.5, 16978.9)
	Negative[e]	Prevax	40	881.9 (601.6, 1292.7)	64	1028.9 (795.8, 1330.3)
		1 Month	40	8386.3 (6235.4, 11279.2)	64	5230.2 (4357.9, 6277.2)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; N/A = not applicable; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.
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 titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 08JAN2023 (20:49)
(Data cutoff date : C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_gmt_sub_1m_ev1_c2f

GMFR

Within baseline positive or baseline negative groups, Omicron BA.4/BA.5 GMFRs at 1 month after study vaccination were:

- Similar in participants 12 through 17 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg group compared with other age and vaccine groups at 1 month after vaccination.
- Higher in participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30- and 60 µg groups compared with participants in the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups. The differences between BNT162b2 Bivalent (WT/OMI BA.4/BA.5) groups and BNT162b2 Bivalent (WT/OMI BA.1) were more substantial in the baseline negative groups.
- Generally similar in participants 18 through 55 and >55 years of age who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either dose.
- Generally similar between the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30- and 60-µg groups.
- Generally similar across both sexes within each age and dose group.

Table 20. Geometric Mean Fold Rises From Before Study Vaccination to Each Subsequent Time Point – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		C4591031 BNT162b2 Bivalent (WT/OMI BA.1)	
Assay	**Dosage/Age Group**	**Sampling Time Point[a]**	**n[b]**	**GMFR[c] (95% CI[c])**	**n[b]**	**GMFR[c] (95% CI[c])**
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	30 µg/12-17 years	1 Month	25	17.8 (11.5, 27.5)	N/A	N/A
	30 µg/18-55 years	1 Month	32	18.9 (12.8, 27.8)	67	9.3 (7.2, 12.1)
	60 µg/18-55 years	1 Month	23	22.9 (13.9, 37.8)	30	8.7 (5.5, 13.5)
	30 µg/>55 years	1 Month	40	22.3 (14.3, 34.6)	63	5.8 (4.5, 7.5)
	60 µg/>55 years	1 Month	31	21.0 (11.8, 37.4)	65	8.4 (6.1, 11.4)
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	30 µg/12-17 years	1 Month	25	11.2 (7.3, 17.0)	N/A	N/A
	30 µg/18-55 years	1 Month	32	17.3 (11.1, 26.9)	67	13.5 (10.3, 17.7)
	60 µg/18-55 years	1 Month	23	17.9 (11.5, 27.8)	30	11.6 (6.9, 19.6)
	30 µg/>55 years	1 Month	40	17.5 (12.2, 25.1)	64	8.2 (6.1, 11.2)
	60 µg/>55 years	1 Month	29	17.8 (10.9, 29.2)	64	9.7 (6.8, 13.9)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	30 µg/12-17 years	1 Month	25	5.3 (3.7, 7.7)	N/A	N/A
	30 µg/18-55 years	1 Month	32	14.1 (9.1, 22.0)	67	6.6 (5.2, 8.3)
	60 µg/18-55 years	1 Month	23	13.5 (7.9, 23.1)	30	6.1 (3.9, 9.5)
	30 µg/>55 years	1 Month	40	9.5 (6.4, 14.0)	64	5.1 (3.9, 6.5)
	60 µg/>55 years	1 Month	31	14.6 (8.4, 25.5)	64	5.0 (3.7, 6.9)

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; N/A = not applicable; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.
Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection)
and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. 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.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 08JAN2023 (21:15)
(Data cutoff date : C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_gmfr_1m_wo_evl_c2f

Seroresponse

Within baseline positive or baseline negative groups, Omicron BA.4/BA.5 seroresponse rates at 1 month after study vaccination were:

- Similar in participants 12 through 17 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared with other age and vaccine groups.
- Similar or higher in participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg and 60-µg groups compared with the corresponding BNT162b2 Bivalent (WT/OMI BA.1) age and dose groups. The higher seroresponse rates in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) groups than the BNT162b2 Bivalent (WT/OMI BA.1) groups were more prominent in the baseline negative groups and the >55 years of age groups.
- Generally similar between the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30- and 60-µg groups.
- Generally similar across both sexes within each age and dose group.

Table 21. Number (%) of Participants Achieving Seroresponse – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		C4591031 BNT162b2 Bivalent (WT/OMI BA.1)	
Assay	Dosage/Age Group	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 – NT50 (titer)	30 µg/12-17 years	1 Month	25	24 (96.0) (79.6, 99.9)	N/A	N/A
	30 µg/18-55 years	1 Month	32	26 (81.3)	67	47 (70.1)

				(63.6, 92.8)		(57.7, 80.7)
	60 µg/18-55 years	1 Month	23	20 (87.0) (66.4, 97.2)	30	19 (63.3) (43.9, 80.1)
	30 µg/>55 years	1 Month	40	36 (90.0) (76.3, 97.2)	63	31 (49.2) (36.4, 62.1)
	60 µg/>55 years	1 Month	31	24 (77.4) (58.9, 90.4)	65	40 (61.5) (48.6, 73.3)
SARS-CoV-2 neutralization assay - Omicron BA.1 – NT50 (titer)	30 µg/12-17 years	1 Month	25	23 (92.0) (74.0, 99.0)	N/A	N/A
	30 µg/18-55 years	1 Month	32	23 (71.9) (53.3, 86.3)	67	59 (88.1) (77.8, 94.7)
	60 µg/18-55 years	1 Month	23	20 (87.0) (66.4, 97.2)	30	22 (73.3) (54.1, 87.7)
	30 µg/>55 years	1 Month	40	37 (92.5) (79.6, 98.4)	64	44 (68.8) (55.9, 79.8)
	60 µg/>55 years	1 Month	29	27 (93.1) (77.2, 99.2)	64	44 (68.8) (55.9, 79.8)
SARS-CoV-2 neutralization assay - reference strain – NT50 (titer)	30 µg/12-17 years	1 Month	25	16 (64.0) (42.5, 82.0)	N/A	N/A
	30 µg/18-55 years	1 Month	32	26 (81.3) (63.6, 92.8)	67	48 (71.6) (59.3, 82.0)
	60 µg/18-55 years	1 Month	23	21 (91.3) (72.0, 98.9)	30	18 (60.0) (40.6, 77.3)
	30 µg/>55 years	1 Month	40	30 (75.0) (58.8, 87.3)	64	35 (54.7) (41.7, 67.2)
	60 µg/>55 years	1 Month	31	24 (77.4) (58.9, 90.4)	64	34 (53.1) (40.2, 65.7)

Abbreviations: LLOQ = lower limit of quantitation; N/A = not applicable; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.

Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up 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 a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥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 both the pre-vaccination time point and the given sampling time point. These values are the denominators for the percentage calculations.

c. n = Number of participants with seroresponse for the given assay at the given sampling time point.

d. Exact 2-sided CI, based on the Clopper and Pearson method.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 10JAN2023 (20:33) (Data cutoff date : C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_sero_1m_wo_evl_c2f

Overall, immune responses against Omicron BA.1 and the reference strain were comparable for both bivalent vaccines in baseline positive participants, and a trend of higher increases for baseline negative participants was observed in participants who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5). Variability in the immune responses were observed for participants in the 2 age groups who received BNT162b2 Bivalent

(WT/OMI BA.4/BA.5) and could relate to smaller number of participants in each group. There is also an increasingly heterogeneous population regarding SARS-CoV-2 infection history and the specific variant responsible for the prior infection(s), which can influence the degree of pre-existing immunity to a given variant. These and additional unmeasured factors may, in part, have contributed to the variable patterns observed across the age groups or vaccine groups for Omicron BA.1 and reference strain-neutralizing titers.

Increased neutralizing responses with BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and BNT162b2 Bivalent (WT/OMI BA.1) were observed regardless of baseline SARS-CoV-2 infection status, with the greatest GMFRs observed in participants without prior infection and the higher neutralizing titers observed in participants with prior infection.

An additional immunogenicity analysis of a subset of BNT162b2-experienced adults 18 through 55 and >55 years of age in C4591044 Cohort 2 who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared with BNT162b2-experienced adults >55 years of age in C4591031 Substudy E who received BNT162b2 30 µg as a booster (fourth) dose was performed. Substantially higher Omicron BA.4/BA.5-specific neutralization titers and higher reference-strain neutralization titers 1 month after study vaccination were reported for participants in both age groups who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared with an adult comparator group from C4591031 Substudy E (>55 years of age) who received a booster dose of BNT162b2 at the 30-µg dose level.

In a separate analysis of a subset of the Cohort 2 immunogenicity population who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg, the vaccine elicited consistently higher Omicron BA.4.6-, BA.2.75.2-, BQ.1.1-, and XBB-specific neutralization titers at 1 month post-vaccination in participants >55 years of age compared with an adult comparator group (>55 years of age) from C4591031 Substudy E who received a booster dose of BNT162b2 at the 30-µg dose level. Immune responses against Omicron XBB variant were more limited compared with the other sublineages.

Combined Cohort 2 (Groups 2 and 4) and Cohort 3 (≥18 Years of Age)

- **Immunogenicity results**

Analysis of immunogenicity data at 1 month after vaccination in the evaluable immunogenicity population with or without evidence of infection up to 1 month after study vaccination for BNT162b2-experienced participants 18 through 55 years and >55 years of age who received a booster (fourth dose) with BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 µg demonstrated a robust vaccine-elicited immune response.

- Superiority of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg to BNT162b2 30 µg in the >55-year age group from C4591031 Substudy E with respect to anti-Omicron BA.4/BA.5 neutralizing titers was met. Noninferiority based on seroresponse for BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg to BNT162b2 30 µg in the >55 years of age was also met.

- Noninferiority of anti-reference-strain immune response based on geometric mean ratio of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg to BNT162b2 30 µg in the >55 years age group was met.

- Noninferiority of the anti-Omicron BA.4/BA.5 response based on GMR and seroresponse for Bivalent BNT162b2 (WT/OMI BA.4/BA.5) participants 18 through 55 in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30- µg group to participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30- µg group were met.

Table 22. Model-Based Geometric Mean Ratios – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)						Vaccine Group Comparison	Age Group Comparison
		C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg		> 55 Years BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg / BNT162b2 30 µg	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg 18-55 Years / >55 Years
		18-55 Years		>55 Years		>55 Years			
Assay	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	GMR[d] (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	1 Month			282	3373.4 (3000.3, 3793.0)	273	1160.7 (1030.3, 1307.7)	2.91 (2.45, 3.44)	
	1 Month	294	4254.2 (3779.6, 4788.4)	282	4344.4 (3850.2, 4902.1)				0.98 (0.83, 1.16)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	1 Month			284	15361.6 (14082.9, 16756.5)	287	11117.2 (10196.4, 12121.1)	1.38 (1.22, 1.56)	

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. 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.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of logarithmically transformed neutralizing titers using a linear regression model with terms of baseline neutralizing titer (log scale) and vaccine group or age group. A separate model was fit for each comparison. Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on the same regression model as stated above.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (01:57)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_gmr_mb_1m_evl_c23

- The proportion of participants who achieved a seroresponse to Omicron BA.4/BA.5 at 1 month after study vaccination was substantially higher for participants 18 through 55 years of age and >55 years of age compared with participants 18 through 55 and >55 years of age in the BNT162b2 30-µg group.

Table 23. Adjusted Difference in Percentages of Participants With Seroresponse – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)						Vaccine Group Comparison	Age Group Comparison
		C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg		> 55 Years BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg / BNT162b2 30 µg	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg 18-55 Years / >55 Years
		18-55 Years		>55 Years		>55 Years			
Assay	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	Difference%[e] (95% CI[f]))	Difference%[e] (95% CI[f]))
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	1 Month	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)	26.77 (19.59, 33.95)	-3.03 (-9.68, 3.63)

Abbreviations: LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
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.
a. Protocol-specified timing for blood sample collection.
b. 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. This value is the denominator for the percentage calculation.
c. n = Number of participants with seroresponse for the given assay at the given sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage.
2-Sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median) for the difference in proportions. The median of baseline neutralizing titers was calculated based on the pooled data in 2 comparator groups.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (01:57)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_dif_mb_1m_evl_c23

- The observed Omicron BA.4/BA.5 neutralizing GMTs at 1 month after study vaccination were substantially higher for participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared with participants 18 through 55 and >55 years of age in the BNT162b2 30-µg group.

Table 24. Geometric Mean Titers, by Subgroup – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
			18-55 Years		>55 Years		>55 Years	
Assay	**Subgroup**	**Sampling Time Point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	All	Prevax	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)	278	205.4 (170.3, 247.7)
		1 Month	297	4455.9 (3851.7, 5154.8)	284	4158.1 (3554.8, 4863.8)	282	938.9 (802.3, 1098.8)
	Baseline SARS-CoV-2 status							
	Positive[d]	Prevax	210	1181.4 (1005.3, 1388.3)	174	1291.7 (1027.5, 1623.8)	40	1939.2 (1326.0, 2835.8)
		1 Month	213	6031.6 (5203.9, 6991.0)	176	6688.9 (5664.4, 7898.8)	40	4772.5 (3413.9, 6671.9)
	Negative[e]	Prevax	84	91.9 (71.5, 118.1)	110	88.9 (69.8, 113.4)	236	139.7 (118.0, 165.3)
		1 Month	84	2067.7 (1530.2, 2793.9)	108	1916.2 (1489.5, 2465.1)	240	718.5 (617.5, 836.0)
	Sex							

	Male	Prevax	103	579.3 (429.9, 780.8)	128	367.9 (263.7, 513.3)	129	219.0 (163.9, 292.7)
		1 Month	104	4261.9 (3431.3, 5293.5)	129	4177.1 (3353.5, 5203.0)	129	957.0 (753.7, 1215.3)
	Female	Prevax	191	564.4 (441.9, 720.8)	156	548.6 (402.3, 748.0)	149	194.2 (151.8, 248.5)
		1 Month	193	4564.0 (3764.1, 5533.9)	155	4142.3 (3311.7, 5181.3)	153	923.9 (748.3, 1140.7)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	All	Prevax	296	4017.3 (3430.7, 4704.1)	284	3690.6 (3082.2, 4419.0)	287	2699.9 (2291.7, 3180.9)
		1 Month	296	16323.3 (14686.5, 18142.6)	286	16250.1 (14499.2, 18212.4)	289	10415.5 (9366.7, 11581.8)
	Baseline SARS-CoV-2 status							
	Positive[d]	Prevax	213	7068.6 (6251.9, 7992.0)	174	8082.1 (6843.6, 9544.8)	41	14247.2 (10299.1, 19708.6)
		1 Month	212	19076.6 (17056.5, 21336.0)	176	21273.3 (18604.2, 24325.3)	41	21444.4 (17318.3, 26553.5)
	Negative[e]	Prevax	83	942.3 (705.6, 1258.3)	110	1068.0 (835.9, 1364.6)	244	2054.8 (1749.9, 2412.8)
		1 Month	84	11014.6 (8793.9, 13796.0)	110	10560.6 (8827.1, 12634.5)	246	9286.4 (8296.8, 10394.0)
	Sex							
	Male	Prevax	103	4063.1 (3178.7, 5193.7)	129	3326.9 (2586.0, 4280.1)	134	2855.0 (2246.0, 3629.0)
		1 Month	104	16565.7 (14039.5, 19546.5)	129	16187.3 (13769.9, 19029.1)	134	11087.9 (9562.7, 12856.4)
	Female	Prevax	193	3993.0 (3252.6, 4902.0)	155	4023.4 (3112.7, 5200.5)	153	2571.1 (2049.3, 3225.7)
		1 Month	192	16193.5 (14119.1, 18572.8)	157	16301.9 (13874.8, 19153.4)	155	9867.2 (8475.9, 11486.9)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
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 titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (02:00)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_gmt_sub_1m_evl_c23

- GMFRs at 1 month after study vaccination were higher for participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups compared with participants 18 through 55 and >55 years in the BNT162b2 30-µg group.

Table 25. Geometric Mean Fold Rises From Before Study Vaccination to Each Subsequent Time Point, by Subgroup – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
			18-55 Years		>55 Years		>55 Years	
Assay	Subgroup	Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	All	1 Month	294	7.8 (6.7, 9.2)	282	8.9 (7.5, 10.6)	273	4.6 (4.0, 5.2)
	Baseline SARS-CoV-2 status							
	Positive[d]	1 Month	210	5.1 (4.4, 6.0)	174	5.2 (4.3, 6.3)	39	2.4 (1.8, 3.2)
	Negative[e]	1 Month	84	22.5 (17.1, 29.6)	108	21.5 (16.6, 27.9)	232	5.1 (4.4, 5.9)
	Sex							
	Male	1 Month	103	7.4 (5.6, 9.7)	128	11.3 (8.7, 14.8)	125	4.4 (3.6, 5.4)
	Female	1 Month	191	8.1 (6.6, 9.8)	154	7.3 (5.8, 9.2)	148	4.7 (3.9, 5.6)
SARS-CoV-2 neutralization assay - reference strain - NT50	All	1 Month	295	4.1 (3.6, 4.6)	284	4.4 (3.8, 5.1)	287	3.9 (3.4, 4.4)

(titer)							
Baseline SARS-CoV-2 status							
Positive[d]	1 Month	212	2.7 (2.4, 3.0)	174	2.7 (2.3, 3.0)	41	1.5 (1.2, 1.9)
Negative[e]	1 Month	83	11.6 (9.0, 15.0)	110	9.9 (7.8, 12.5)	244	4.5 (4.0, 5.2)
Sex							
Male	1 Month	103	4.1 (3.2, 5.1)	129	4.9 (3.9, 6.0)	134	3.9 (3.2, 4.7)
Female	1 Month	192	4.1 (3.4, 4.8)	155	4.1 (3.4, 5.0)	153	3.9 (3.2, 4.6)

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. 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.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (01:40)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_gmfr_sub_1m_evl_c23

These results suggest an anticipated improved clinical benefit against COVID-19 due to Omicron BA.4/BA.5 with BNT162b2 Bivalent (WT/OMI BA.4/BA.5) compared with BNT162b2 as a booster (fourth dose).

2.6.3. Discussion on clinical efficacy

This application concerns the extension of indication of the Comirnaty Original/Omicron BA.4-5 to add a new strength (1.5/1.5 µg) as a primary series (3 doses) and a booster dose for children 6 months up to less than 5 years of age.

Comirnaty Original 3 µg has been approved since October 2022 for this age group. The approval of the Original 3 µg vaccine was based on data from a randomized, observer blinded placebo-controlled trial. The VE after 3 doses in age group 6 m -<5y was 80.3 % (95% CI 13.9, 96.7). The MAH has not applied for a booster indication for Original Comirnaty 3 µg for 6m-<5y.

Antibodies elicited by the Original strain vaccine provide lower and short-lived protection against the Omicron strains as randomized clinical trials and observational data from all over the world have indicated. In response to the waning protection, the MAH updated the COVID-19 vaccine to a bivalent formulation to include both the Reference and Omicron strains. The first bivalent formulation Original/Omicron BA.1 15/15 µg received a booster indication for individuals 12 years and older in September 2022. The immunogenicity was evaluated in subjects older than 55 years, where approximately 230 individuals in each study arm received either Original, monovalent or bivalent vaccine including Omicron BA.1 as 4th dose. Superiority of Original/Omicron BA.1 (15/15 µg) was demonstrated over Original (30 µg) in sense of antibody titer against

BA.1 (GMR 1.56, 95% CI 1.17, 2.08), whereas the level of anti- reference strain antibodies did not differ between study arms.

The bivalent formulation including Omicron BA.4-5 strain received a booster indication for age groups 12 and older (15/15 µg) and for 5 to <12 years old (5/5 µg) later in autumn 2022. There were no clinical immunogenicity data available at the time of approval. Instead, the efficacy and immunogenicity were extrapolated from studies with the bivalent vaccine Original/Omicron BA.1 and with Original Comirnaty.

Currently submitted data comes from studies investigating Original /Omicron BA 4-5 as a fourth dose after 3 doses of Original Comirnaty. No data from primary series with the bivalent vaccine has been submitted. The MAH has shown earlier plans to investigate a primary series in the youngest age group, the study is ongoing.

Age group 6m-<5y. Pivotal data.

No dose-response study has been presented for the Original /Omicron BA 4-5 (1.5/1.5 µg) vaccine. The lowest dose in the Original vaccine study was 3 µg and the MAH does not currently have immunogenicity data from a primary series with the bivalent vaccine. Although there is no immunogenicity data of 1.5 µg mRNA, as the total amount in the bivalent vaccine are 3 µg, the immunogenicity is considered to be at the same level as for the Original Comirnaty 3 µg.
The MAH complemented that the C4591048 substudy A which investigates the immunogenicity of a primary series of Original /Omicron BA 4-5 (1.5/1.5 µg) is ongoing and as of 01 Jun 2023, Substudy A Phase 1 has completed enrolment in the 6 months to <2 years cohort (target n = 90) and has reached 75% (64 out of 90) of the enrolment target in the 2 to <5-year-old group. The MAH has committed to submit this data as soon as available.

Substudy B of C4591048 is an open-label study to evaluate the safety, tolerability, and immunogenicity of a third or fourth dose with the bivalent BNT162b2 (Original/Omi BA.4-5) at 3 µg (1.5/1.5 µg). As there is no placebo arm in the study and no efficacy will be evaluated, the open-label format is acceptable.

Approximately 300 participants in Group 2, ≥6 months to <5 years of age, who have received 3 prior doses of BNT162b2 3 µg, with their last dose 60 to 240 days prior to enrolment, will receive 1 dose (fourth) of bivalent BNT162b2 (Original/Omi BA.4-5) 3 µg. The study is powered for superiority and non-inferiority evaluation, this data will be submitted later when the study is finalized, the interim CSR with safety and immunogenicity for the entire Subgroup B (N = 300) is targeted for end of June 2023.

In the current report a 1-month post dose descriptive immunogenicity data is presented for a subset of 60 participants in Group 2 of C4591048 Substudy B (the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively). Results include also data from a comparator subset of 60 participants ≥6 months to <5 years of age (24 and 36 participants ≥6 months to <2 years of age and ≥2 years to <5 years of age, respectively) in Study C4591007 who received 3 doses of BNT162b2 at 3 µg. The sample size presented currently comprise 60 individuals but as the data are descriptive and a larger cohort will be analysed later, the current sample size is acceptable. The time since last dose was 2-8 months. About 70 % of subjects had no history of previous COVID-19. Data for the same number of doses was presented for adults (supportive studies).

The baseline antibody level against the reference strain was higher in the group allocated to receive a 4th dose than in the group receiving a third dose. In the COVID-19 negative group, baseline anti-reference strain antibody level was more than four-fold higher in the bivalent Original/Omicron BA.4-5 than in the Original. After the booster dose, the anti-reference strain antibodies were in comparable level in all groups independent of the baseline COVID-19 status, antibody level at the baseline or number of earlier doses.

At baseline COVID-19 negative groups, the anti-Omicron BA 4-5 levels were low in both bivalent 4th dose and Original as 3rd dose groups, however GMTs were almost three-fold higher in the bivalent group compared to the original group. GMFR was approximately 14 for bivalent group and for the Original group, 11.

Additionally, in a small subset (N= 31 in each arm) the neutralization against new circulating COVID-19 strains was evaluated using an unvalidated FFRNT assay. The results showed low antibody titers against these new strains both after 3 doses of Original and after the 4th dose of bivalent vaccine. After the 4th dose with bivalent, the antibodies were higher than after 3rd dose with Original, but still remained modest in comparison to the GMTs against targeted strains. The clinical benefit for these modestly higher antibodies is unknown.

In summary, the Original/Omicron BA.4-5 (1.5/1.5 µg) vaccine given as a 4th dose is immunogenic in children 6m-<5 y who have previously received 3 doses of Original 3 µg. There are currently no data on primary vaccination with the bivalent vaccine in any age group although such data are expected. The assumption that the bivalent vaccine will provide sufficient protection when given as a primary vaccination is extrapolated from the demonstrated immunogenicity of the booster dose.

Age group 5-11 years. Supportive data.

Substudy D of C4591048 is a Phase 3 open-label study to evaluate the safety, tolerability, and immunogenicity of a third or fourth dose with bivalent BNT162b2 (Original/Omi BA.4-5) 5/5 µg in approximately 250 participants at ages ≥5 - <12 years, who were previously vaccinated with Original. As in Substudy B, the immunogenicity is compared to a cohort which has received 3 doses of Original 10 µg. No data from primary series from this cohort vaccinated with Original/Omi BA.4-5 (5/5 µg) are available.

The immunogenicity population included approximately 100 individuals in each study arm. This sample size suffices for descriptive immunogenicity analysis. About 60 % of the study population had COVID-19 earlier. The primary endpoint was descriptive GMR of GMTs in the 4th dose bivalent arm and comparison arm with 3 doses of Original only. The MAH used a Model Based Geometric Mean Ratio calculation and explained the methodology behind the GMR calculation. The model based result showed no substantial difference between the 4th dose bivalent arm and 3rd dose Original arm (GMR 1.2 (95% CI 0.92, 1.37)) as the model based Omicron BA.4-5 GMTs were very similar (1836 vs. 1633 respectively). The seroresponse rate to omicron BA.4/5 was also almost identical.

These data show that Original/Omicron BA.4-5 (5/5 µg) is immunogenic as 4th dose in children 5y-<12 y who have previously received 3 doses of Original 10 µg. It is anticipated that this vaccine is immunogenic also as a primary series as half of the amount of mRNA is the same as in the approved Original vaccine and the Omicron BA.4-5 component has been demonstrating immunogenicity as a booster dose.

Age group >12 years. Supportive data.

Study C4591044 is a randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of new bivalent variant vaccines in different age groups: 12-17, 18-55 and >55. The study is divided into cohorts. Immunogenicity in some cohorts was studied only descriptively (Cohort 2), whereas some groups from Cohorts 2 and 3 together were analysed for superiority and non-inferiority.

The immunogenicity population in Cohort 2 were around 100 individuals in each age group, who received a 4th dose with Original/Omicron BA.4-5 30 µg. For descriptive immunogenicity, 100 individuals is acceptable. Combining Cohort 2 and Cohort 3, there were almost 300 individuals in each age group (18-55 and >55). As a comparison arm, approximately 300 individuals older than 55 who had received a 4th dose of Original 30 µg in study C4591031, were selected. This comparison arm is valuable as all study participants have received

the same number (4) of doses as in the active arm. The sample size about 300 individuals in each arm is sufficient for the superiority and non-inferiority testing.

The descriptive data from Cohort 2 demonstrated the immunogenicity of a 4th dose with Original/Omicron BA.4-5 in all studied age groups in terms of raised GMTs. The hypothesis analyses were conducted in the combined cohorts 2 and 3. The MAH used the same model based calculation for GMRs as in study C4591048 SSD. These results were presented in Table 23 and the MAH has explained that the model based GMT values of >55 years Original/Omicron BA.4-5 vaccine group participants depend on the comparator group. The MAH also explained that the GMR originates from model based GMT calculation, which is considered as an intermediate estimate in order to reach a more valid and meaningful model-based GMR. If presented together in the product information, descriptive GMTs and model- based GMTs for the same groups would be confusing, therefore the presentation of descriptive non adjusted GMTs and model based GMR in the same table has been agreed.

The model-based GMR showed superiority (GMR 2.91 95% CI 2.45; 3.44) of antibody titer against Omicron BA. 4-5 after a 4th dose with the bivalent Original/Omicron BA. 4-5 vaccine (15/15 µg) compared to 4th dose with Original 30 µg vaccine in the age group older than 55. The non-inferior response to the reference strain was also demonstrated (GMR 1.38; 95% CI 1.22, 1.56). As non-inferiority (GMR 0.98; 95% CI 0.83, 1.16) was demonstrated also for responses to Omicron BA 4-5 between 18-55 and >55 arms in the bivalent group, one can conclude that superiority of the bivalent vaccine to elicit anti Omicron BA. 4-5 response should be anticipated in the entire adult population. The non-inferior seroresponse to Omicron BA.4-5 was met between age groups older or younger than 55 years in study C4591044, but seroresponse in this study age group was higher than in C4591031 Substudy E and non-inferiority was not met (difference 26.77 % (95% CI: 19.59, 33.95)) (*Table 23*).

Descriptive data from Cohorts 2 and 3 showed generally the same result for all age cohorts, including adolescents. There was no comparison group for 12-17 year olds from study C4591031.

These data show that the Original/Omicron BA.4-5 (15/15 µg) vaccine is immunogenic as a 4th dose in individuals older than 12 years of age who have previously received 3 doses of Original 30 µg. It is anticipated that this vaccine is immunogenic also as a primary series as half of the amount of mRNA is the same as in approved Original vaccine and Omicron BA4-5 component has been demonstrating immunogenicity as a booster dose.

2.6.4. Conclusions on clinical efficacy

These data show that Original/Omicron BA.4-5 (1.5/1.5 µg) is immunogenic as a 4th dose in individuals older than 6m to <5 y who have previously received 3 doses of Original 3 µg.

No dose-response study has been presented for the Original /Omicron BA 4-5 (1.5/1.5 µg) vaccine and the lowest dose in the Original study was 3 µg. As altogether the bivalent vaccine contains 3 µg, it is considered that the amount of mRNA is immunogenic. The ongoing Substudy A is investigating a dose-response of Original/Omicron BA.4-5 among children younger than 5 years, data is expected to be submitted as soon as available.

The immunogenicity against newly circulating strains was low and therefore the clinical benefit against new strains is unknown.

2.6.5. Clinical safety

To support the indication of the bivalent COVID-19 vaccine Original/Omicron BA.4-5 administered as a primary series as well as a booster dose at 1.5/1.5µg in subjects aged ≥6 months to <5 years of age, the MAH presented data from a limited number of participants included in the study C4591048 Substudy B Group 2 Subset ≥6 Months to <5 Years of Age. No data where the bivalent vaccine has been administered as a primary series has been provided.

In addition, data from studies C4591048 and C4591044 including subjects ≥5 years of age and ≥12 years of age who have received the bivalent Original/Omicron BA.4-5 vaccine as a booster dose have been provided as supportive data for extrapolation purposes.

The primary series of three doses BNT162b2 Original 3µg for children aged 6 months to <5 years of age was evaluated in the EMEA/H/C/005735/X/0138 procedure.

The studies are described separately below.

2.6.5.1. Study C4591048 Substudy B Group 2 Subset (≥6 Months to <5 Years of Age: Booster (Fourth Dose) With BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 3 µg

One month post forth dose safety data is available for a subset of 60 subjects in this study, cut-off date is 25 November 2022.

The safety population included 24 participants ≥6 months <2 years of age and 36 participants ≥2 years to <5 years of age who received a fourth dose of the bivalent BNT162b2 (Original/Omi BA.4/BA.5) at 3 µg. No participants were excluded from the safety population for any reason and all participants received the fourth dose of vaccine as assigned. Overall, median follow-up time after study vaccination was 1.8 months. Majority of participants (96.7%) completed the 1-month post vaccination visit. No participant in the ≥6 months to <2 years of age group and 1 participant in the ≥2 to <5 years of age group was withdrawn due to personal decision from the study as of the data cut-off date (25 November 2022).

The reactogenicity and antipyretic/pain medication were reported by using an e-diary for 7 days after study vaccination. Grading scales were based on FDA guidance. AEs are collected from the study vaccination up to 1 month after the study vaccination, and serious AEs (SAEs) are collected from study vaccination up to 6 months post-Dose. Reactogenicity was reported as follows:

Children ≥6 months to <2 years of age:
• Local reactions: tenderness, redness, and swelling at the injection site
• Systemic events: fever, decreased appetite, drowsiness, and irritability

Children ≥2 to <5 years of age:
• Local reactions: pain, redness, and swelling at the injection site
• Systemic events: fever, fatigue, headache, chills, vomiting, diarrhoea, new or worsened muscle pain, and new or worsened joint pain

- **Demographics**

≥6 Months to <2 Years of Age
In total, most participants were White (54.2%), with 4.2% Black or African American participants, 20.8% Asian participants, and 20.8% multiracial participants. There were 16.7% Hispanic/Latino participants. Median age was 19 months and 58.3% of participants were female. A total of 41.7% of participants had

evidence of prior SARS-CoV-2 infection ("baseline positive"). Median time since last prior dose of BNT162b2 before study vaccination was 6.4 months. None of the participant received a non-study vaccine after study vaccination as of the data cut-off date.

≥2 to <5 Years of Age

In total, most participants were White (61.1%), with 5.6% Black or African American participants, 11.1% Asian participants, and 22.2% multiracial participants. There were 30.6% Hispanic/Latino participants. Median age was 2.0 years and 55.6% of participants were male. Three (8.3%) participants were reported as obese. A total of 19.4% of participants were baseline positive for prior SARS-CoV-2 infection. Median time since last prior dose of BNT162b2 before study vaccination was 7.1 months. The medical histories of participants at study baseline included conditions and procedures typically observed in the general population for each age group.

Two (5.6%) participants received a non-study vaccine (Influenza vaccine) at least 14 days after study vaccination as allowed per protocol.

Reactogenicity

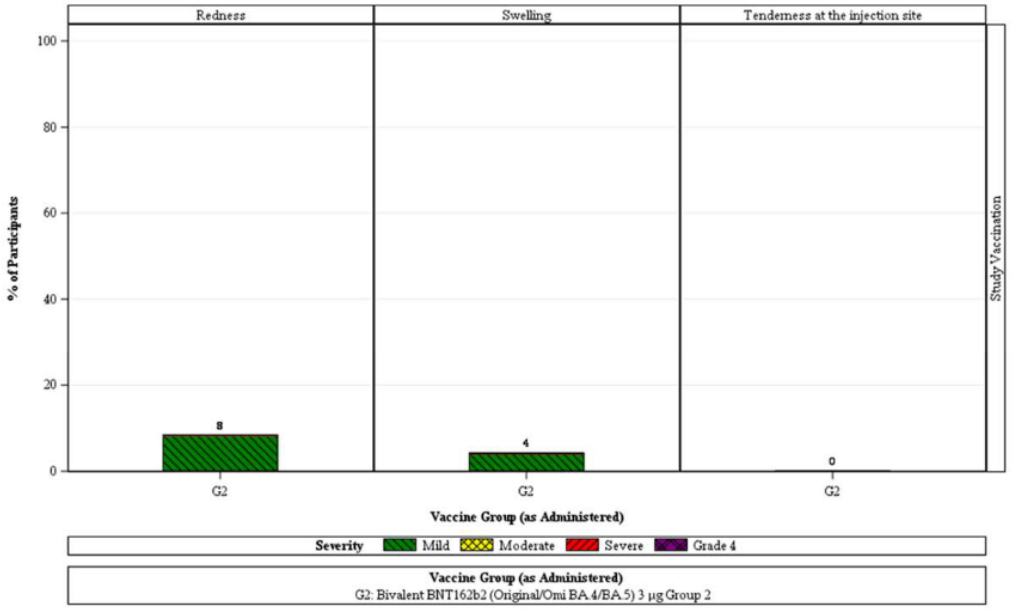
Local reactions

≥6 Months to <2 Years of Age

All local reactions were mild in severity. No moderate, severe, or Grade 4 local reactions were reported. The onset for all local reactions was 1 day and resolved within 1 day after onset.

In this initial subset of 24 participants, the frequencies of local reactions reported within 7 days after the bivalent BNT162b2 (Original/Omicron BA.4-5) at 3 µg vaccine are much lower than the frequencies previously observed in association with the original BNT162b2 vaccine within the respective age group. According to the MAH, this is likely a factor of the small number of participants for this dataset.

Figure 1. Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Subset of Substudy B Group 2 - ≥6 Months to <2 Years of Age – Safety Population



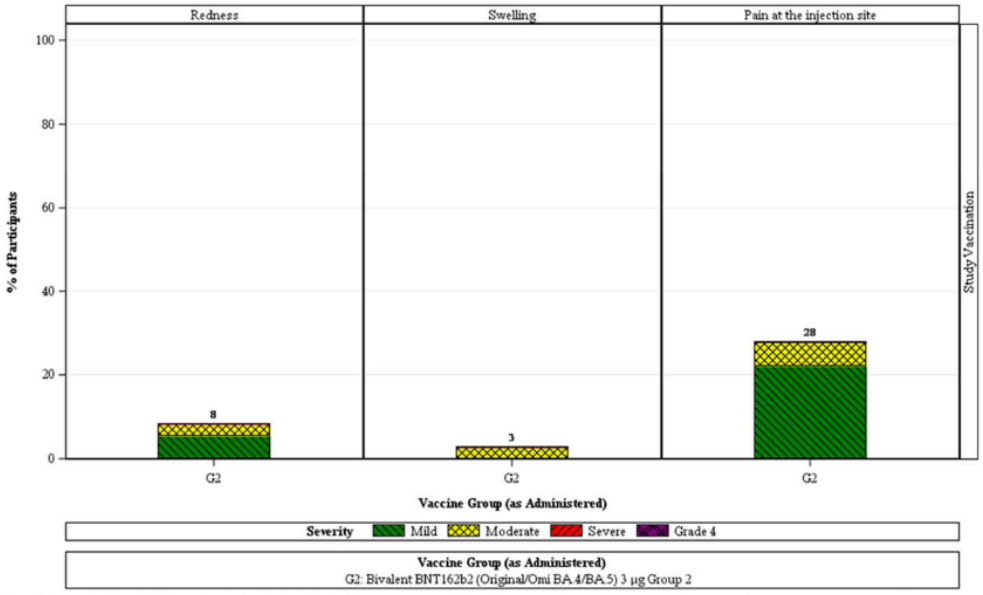
Note: Subset of Substudy B Group 2 includes the first 24 and 36 participants enrolled in 6 months to 2 years age group and 2 years to 5 years age group, respectively.
Note: Substudy B Group 2 includes participants 6 months to 5 years of age who received 3 doses of BNT162b2 3 g 60 to 240 days prior to enrollment.
Note: The number above each bar denotes the percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 08DEC2022 (16:32) Source Data: adfacevd
Table Generation: 13DEC2022 (20:28) (Cutoff Date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: /nda2_ubped2/C4591048_B_1MPD_Safety/adce_f001_lr_p2_6m2y

≥2 to <5 Years of Age

Most local reactions were mild or moderate in severity. No severe or Grade 4 local reactions were reported by any participant in the ≥2 to <5 years of age group who received a fourth dose of the bivalent BNT162b2 (Original/Omicron BA.4-5) at 3 µg. The onset for all local reactions was 1 to 2 days, and all events resolved within 1 to 3 days after onset.

In this initial subset of 36 participants, the frequencies of local reactions reported within 7 days after the bivalent BNT162b2 (Original/Omicron BA.4-5) at 3 µg vaccine are much lower than the frequencies previously observed in association with the original BNT162b2 vaccine within the respective age group. According to the MAH, this is likely a factor of the small number of participants for this dataset.

Figure 2. Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Subset of Substudy B Group 2 - ≥2 to <5 Years of Age – Safety Population



Note: Subset of Substudy B Group 2 includes the first 24 and 36 participants enrolled in 6 months to 2 years age group and 2 years to 5 years age group, respectively.
Note: Substudy B Group 2 includes participants 6 months to 5 years of age who received 3 doses of BNT162b2 3 g60 to 240 days prior to enrollment.
Note: The number above each bar denotes the percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 08DEC2022 (16:32) Source Data: adfacevd
Table Generation: 13DEC2022 (20:28) (Cutoff Date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: /nda2_ubped2/C4591048_B_1MPD_Safety/adce_f001_lr_p2_2y5y

Systemic Events

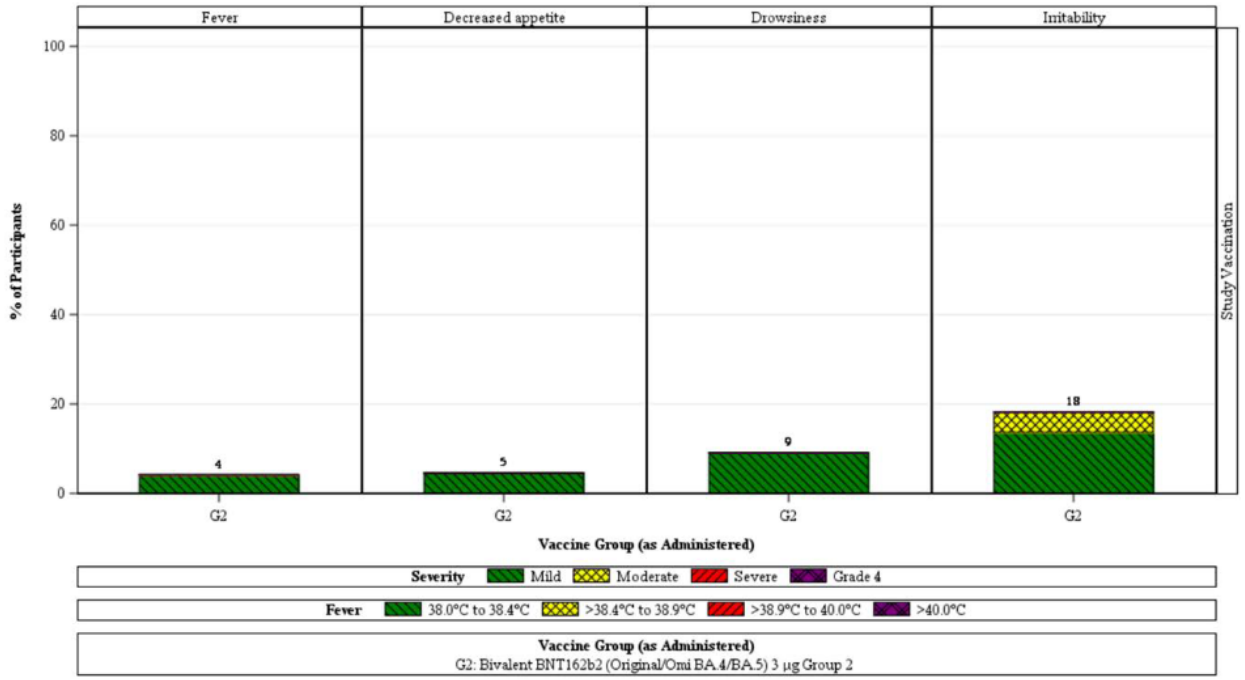
≥6 Months to <2 Years of Age

No participants reported fever >38.4 °C. Antipyretic or pain medication use was reported by 8.3% of participants after study vaccination. Most systemic events were mild or moderate in severity. No severe or Grade 4 systemic events were reported by any participant in the ≥6 months to <2 years of age group who received a fourth dose of the bivalent BNT162b2 (Original/Omicron BA.4-5) at 3 µg.

The median onset for all systemic events was 2 to 6 days, and all events resolved within a median duration of 1 to 3 days after onset.

In this initial subset of 24 participants, the frequencies of systemic reactions reported within 7 days after the bivalent BNT162b2 (Original/Omicron BA.4-5) at 3 µg vaccine are much lower than the frequencies previously observed in association with the original BNT162b2 vaccine within the respective age group. According to the MAH, this is likely a factor of the small number of participants for this dataset.

Figure 3. Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Subset of Substudy B Group 2 - ≥6 Months to <2 Years of Age – – Safety Population



Note: Subset of Substudy B Group 2 includes the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
Note: Severity was not collected for use of antipyretic or pain medication.
PFIZER CONFIDENTIAL SDTM Creation: 08DEC2022 (16:32) Source Data: adfacevd
Table Generation: 19DEC2022 (22:07) (Cutoff Date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: /nda2_ubped2/C4591048_B_1MPD_Safety/adce_f001_se_p2_6m2y

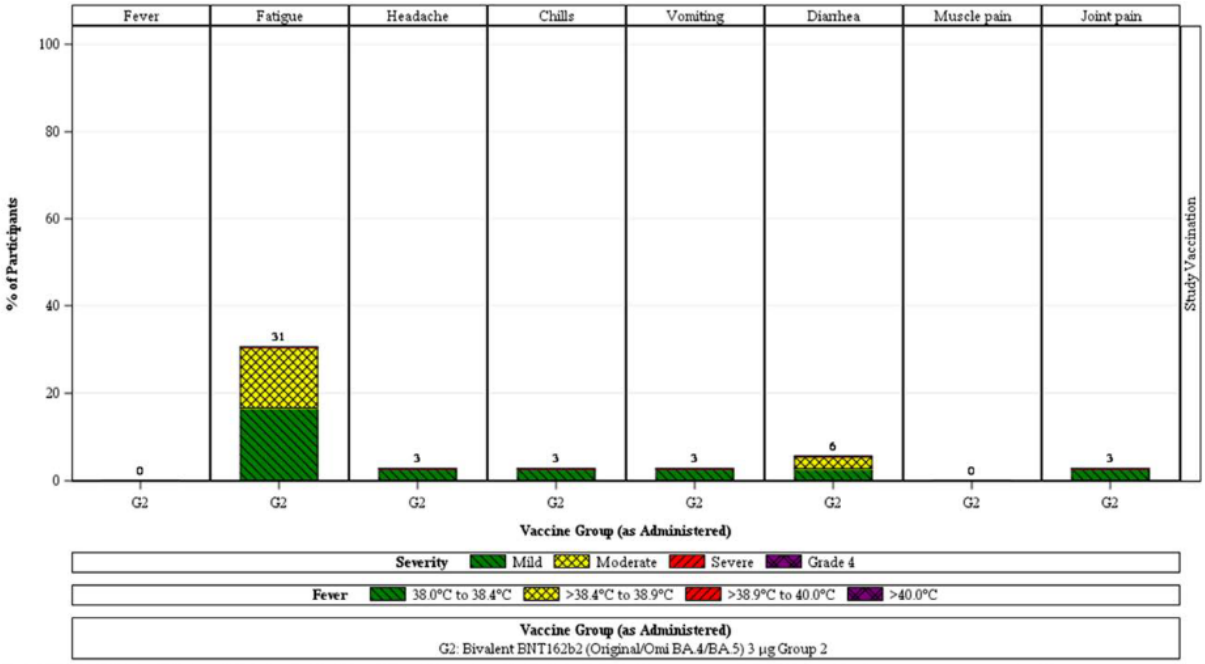
≥2 to <5 Years of Age

Antipyretic or pain medication use was reported by 2.8% of participants after study vaccination.

Most systemic events were mild or moderate in severity. No severe or Grade 4 systemic events were reported by any participant in the ≥2 years to <5 years of age group who received a fourth dose of the bivalent BNT162b2 (Original/Omicron BA.4-5) at 3 µg. The median onset for most systemic events was 1 to 6 days, and most events resolved within a median duration of 1 to 2 days after onset. One participant reported headache and chills, which lasted 24 days.

In this initial subset of 36 participants, the frequencies of systemic reactions reported within 7 days after the bivalent BNT162b2 (Original/Omicron BA.4-5) at 3 µg vaccine are lower than the frequencies previously observed in association with the original BNT162b2 vaccine within the respective age group. According to the MAH, this is likely a factor of the small number of participants for this dataset.

Figure 4. Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Subset of Substudy B Group 2 - ≥2 to <5 Years of Age – Safety Population



Note: Subset of Substudy B Group 2 includes the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
Note: Severity was not collected for use of antipyretic or pain medication.
PFIZER CONFIDENTIAL SDTM Creation: 08DEC2022 (16:32) Source Data: adfacevd
Table Generation: 13DEC2022 (20:28) (Cutoff Date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: /nda2_ubped2/C4591048_B_1MPD_Safety/adce_f001_se_p2_2y5y

Adverse Events

Overall, AEs were reported by 3 (12.5%) and 1 (2.8%) participant in the ≥6 months to <2 years of age group and 2 to <5 years of age group, respectively. No severe, life- threatening, SAEs or AEs leading to withdrawal or death were reported from study vaccination to 1 month after study vaccination. Overall, the AE profile at 1 month post dose was generally similar to that at 7 days post dose.

No additional AEs were reported up to data cut-off date of 25 November 2022.

Table 26.

Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination to 1 Month After the Study Vaccination, by System Organ Class and Preferred Term – Subset of Substudy B Group 2 – ≥6 Months to <5 years of Age – Safety Population

	Vaccine Group (as Administered)					
	Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg					
	≥6 Months to <2 Years (N^a=24)		≥2 to <5 Years (N^a=36)		≥6 Months to <5 Years (N^a=60)	
System Organ Class Preferred Term	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])
Any adverse event	3 (12.5)	(2.7, 32.4)	1 (2.8)	(0.1, 14.5)	4 (6.7)	(1.8, 16.2)
Gastrointestinal disorders	1 (4.2)	(0.1, 21.1)	0	(0.0, 9.7)	1 (1.7)	(0.0, 8.9)
Diarrhoea	1 (4.2)	(0.1, 21.1)	0	(0.0, 9.7)	1 (1.7)	(0.0, 8.9)
General disorders and administration site conditions	2 (8.3)	(1.0, 27.0)	1 (2.8)	(0.1, 14.5)	3 (5.0)	(1.0, 13.9)
Fatigue	1 (4.2)	(0.1, 21.1)	0	(0.0, 9.7)	1 (1.7)	(0.0, 8.9)
Injection site pain	1 (4.2)	(0.1, 21.1)	0	(0.0, 9.7)	1 (1.7)	(0.0, 8.9)
Injection site warmth	0	(0.0, 14.2)	1 (2.8)	(0.1, 14.5)	1 (1.7)	(0.0, 8.9)
Pyrexia	1 (4.2)	(0.1, 21.1)	0	(0.0, 9.7)	1 (1.7)	(0.0, 8.9)
Skin and subcutaneous tissue disorders	0	(0.0, 14.2)	1 (2.8)	(0.1, 14.5)	1 (1.7)	(0.0, 8.9)
Erythema	0	(0.0, 14.2)	1 (2.8)	(0.1, 14.5)	1 (1.7)	(0.0, 8.9)

Note: MedDRA (v25.1) coding dictionary applied.
Note: Subset of Substudy B Group 2 includes the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
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 event. For "any adverse 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: 08DEC2022 (16:31) Source Data: adae Table Generation: 13DEC2022 (20:27)

Immediate Adverse Events

No participant in the ≥6 months to <2 years and ≥2 to <5 years of age groups were reported to have an immediate AE within 30 minutes of study vaccination.

Related Adverse Events

AEs assessed by the investigator as related were reported by 1 (4.2%) participant in the ≥6 months to <2 years of age group. These events were consistent with reactogenicity events and included fatigue (n=1) and injection site pain (n=1)

Severe or Life-Threatening Adverse Events

No severe or life-threatening AEs were reported from study vaccination through 1 month post vaccination.

Deaths and Serious Adverse Events

No deaths or SAEs were reported by participants in the ≥6 months to <2 years of age group and ≥2 years to <5 years of age group from study vaccination through 1 month post vaccination.

Adverse Events Leading to Withdrawal

There were no discontinuations due to AEs reported from study vaccination through 1 month post vaccination for participants in the ≥6 months to <2 years of age group and ≥2 years to <5 years of age group.

Other Significant Adverse Events

Some AEs are of specific interest due to their autoimmune or neuroinflammatory nature, theoretical association with vaccines, or known occurrence in patients with COVID-19. From study vaccination through 1 month post dose, no AEs of lymphadenopathy, rash, anaphylaxis/hypersensitivity, appendicitis, Bell's palsy, and myo/pericarditis were reported up to 1 month post vaccination.

MAH Conclusion

Based on the available safety data from a subset of 60 participants (the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively) from study vaccination through 1-month post study vaccination, the bivalent BNT162b2 (Original/Omi BA.4/BA.5) at the 3 µg dose level was generally well tolerated across both age groups (≥6 months to <2 years of age and ≥2 to <5 years of age), with mostly mild or moderate reactogenicity and few reported AEs. No new adverse reactions were identified based on the available data from this data cut.

In this initial subset of 60 participants, the frequencies of local and systemic reactions reported within 7 days after the bivalent BNT162b2 (Original/Omi BA.4/BA.5) at 3 µg vaccine are lower than the frequencies previously observed in association with the original BNT162b2 vaccine within the respective age group. This is likely a factor of the small number of participants for this dataset.

The incidence of any AEs within 1 month post study vaccination was low (n=4). No immediate AEs, severe AEs, SAEs, or AEs leading to withdrawal were reported. No AEs of clinical interest were reported (eg, anaphylaxis/hypersensitivity, appendicitis, Bell's palsy, myo/pericarditis). No new or concerning safety findings were noted in this subset of 60 participants up to at least 1 month post vaccination data.

Based on the safety data up to 1 month post vaccination with the bivalent BNT162b2 (Original/Omicron BA.4-5) at the 3 µg dose level in these 60 Study C4591048 participants ≥6 months to <2 years and ≥2 years to <5 years of age, the Original/Omicron BA.4-5 bivalent vaccine appears to be safe and tolerable in this population with no significant new safety information identified in this age group.

2.6.5.2. Study C4591048 Substudy D Group 2 (≥5 to <12 Years of Age): Booster (Fourth Dose) With BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 10 µg

The study is further described in EMEA/H/C/005735/II/0177/G procedure where the use of the bivalent Original/Omicron BA.4-5 vaccine (5/5µg) was evaluated for use as primary series.

- The safety population included 113 participants ≥5 years to <12 years of age who received a fourth dose with BNT162b2 Bivalent (Original/Omicron BA.4-5) at 10 µg. Median follow-up time after study vaccination was 1.6 months. Cut-off date was 25 Nov 2022.
- The safety profile within 1 month after study vaccination (fourth dose) with bivalent Original/Omicron BA.4-5 vaccine at the 10µg (5/5 µg) was generally well tolerated, with mostly mild or moderate reactogenicity and few reported AEs. No new adverse reactions were identified based on the available data from this data cut.
- The reactogenicity profile within 7 days after administration of bivalent Original/Omicron BA.4-5 vaccine at the 10µg (5/5 µg) was generally similar to that previously observed in association with administration of BNT162b2 Original 10µg in this age group.

- The AE profile within 1 month after study vaccination was consistent with the known safety profile of BNT162b2 Original. Incidence of AEs, including severe AEs, was low. No immediate AEs, SAEs, or AEs leading to withdrawal were reported. One male participant between 10 and 17 years of age reported an event of lymph node palpable (left axillary lymph node palpable) of moderate severity with onset on Day 2 after study vaccination that resolved within 3 days. The event was assessed by the investigator as related to study intervention. Other than this 1 case of lymph node palpable, no other AEs of clinical interest were reported (eg, rash, anaphylaxis/hypersensitivity, appendicitis, Bell's palsy, myo/pericarditis). No new or concerning safety findings were noted in these 113 participants up to 1 month of post vaccination data.
- Based on the safety data up to 1-month after study vaccination with bivalent Original/Omicron BA.4-5 vaccine at the 10µg (5/5µg) in 113 participants in study C4591048 participants ≥5 years to <12 years of age, the bivalent Original/Omicron BA.4-5 vaccine at the 10µg (5/5µg) appears to be consistent with the known safety profile of BNT162b2.

2.6.5.3. Study C4591044 Cohorts 2 (≥12 Years of Age) and 3 (≥18 Years of Age): Booster (Fourth Dose) of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 or 60 µg

This study was previously evaluated in EMEA/H/C/005735/MEA/059.1 and is also described in the EMEA/H/C/005735/II/0177/G procedure.

- In Cohort 2 (All Groups), the safety population included 528 participants ≥12 years of age who received a booster (fourth dose) with BNT162b2 Bivalent Original/Omicron BA.4-5 at 30 or 60 µg. In combined Cohort 2 (Groups 2 and 4) and Cohort 3, the safety population included 619 participants who received BNT162b2 Bivalent Original/Omicron BA.4-5 at 30 µg: 313 participants who were 18 through 55 years of age and 306 participants who were >55 years of age; median follow-up time after study vaccination to the data cut off (12 Oct 2022) or withdrawal date across vaccine groups was 1.5 months.
- The safety profile within 1 month after vaccination (Dose 4) with BNT162b2 Bivalent Original/Omicron BA.4-5 at the 30-µg dose level was well tolerated across all age groups, with mostly mild or moderate reactogenicity and few reported AEs.
- The reactogenicity profile within 7 days after BNT162b2 Bivalent Original/Omicron BA.4-5 vaccine was generally similar to that previously observed in association with booster doses of an Omicron BA.1-modified BNT162b2 bivalent vaccine and to BNT162b2 Original within the respective age groups at the same dose. Both local reactions and systemic events for participants who received the 30-µg dose level tended to be lower for adults >55 years of age compared with younger adult participants (18 through 55 years of age). There was an observed dose dependency for reactogenicity between the BNT162b2 bivalent Original/Omicron BA.4-5 where 30- and 60-µg groups with most local reactions and systemic events reported more frequently after a 60-µg dose, which is consistent with prior observations for BA.1-modified bivalent and monovalent vaccines.
- The AE profile within 1 month after vaccination consisted of reactogenicity events, labelled reactions (eg, lymphadenopathy, arthralgia), and other AEs that occur in a general adult population. Incidence of lymphadenopathy, severe AEs, and SAEs was low. No life-threatening (Grade 4) events were reported. No new or concerning safety findings were noted 1 month after vaccination.

2.6.5.4. Post marketing experience

No post authorization safety data for BNT162b2 Bivalent (Original/Omicron BA.4-5) in subjects aged ≥6 months to <5 years of age has been provided. The MAH will continue to monitor all emerging post authorization safety data for BNT162b2 Bivalent (Original/Omicron BA.4-5) for pharmacovigilance and risk management purposes.

2.6.6. Discussion on clinical safety

To support the indication of the bivalent COVID-19 vaccine Original/Omicron BA.4-5 administered as a primary series as well as a booster dose at 1.5/1.5µg in subjects aged ≥6 months to <5 years of age, the MAH has presented data from a limited number (n=60) of participants included in the study C4591048 Substudy B Group 2 Subset ≥6 Months to <5 Years of age. These subjects are divided into two subgroups based on age: 24 participants ≥6 months <2 years of age and 36 participants ≥2 years to <5 years of age. Both groups received a fourth dose of the bivalent BNT162b2 (Original/Omicron BA.4-5) at 1.5/1.5 µg. No data where the bivalent vaccine has been administered as a primary series has been provided.

In addition, data from studies C4591048 and C4591044 including subjects ≥5 years of age and ≥12 years of age who has received the bivalent Original/Omicron BA.4-5 vaccine as a booster dose have been provided as supportive data for extrapolation purposes.

Study C4591048 Substudy B

The 60 subjects are presented into two subgroups based on age: 24 participants ≥6 months <2 years of age and 36 participants ≥2 years to <5 years of age. Both groups received a fourth dose of the bivalent BNT162b2 (Original/Omicron BA.4-5) vaccine at 1.5/1.5 µg. No subjects were excluded based on safety reasons. One-month post vaccination visit was completed by around 97% of the subjects and the median follow-up time after the booster dose was 1.8 months. More than half of the participants in both age groups were white. In the youngest age group 58% of participants were female and among the older children 56% were male. Median time since last prior dose of BNT162b2 Original was 6.4-7.1 months for the younger and older age groups, respectively . Baseline positive for SARS-CoV-2 infection was noted among 42% in the youngest group and in 19% of the older children.

Reactogenicity: Few and mild local reactions were reported among the 24 children aged ≥6 months <2 years who received Original/Omicron BA.4-5 3µg as a fourth dose. Redness was reported among 8% of the subjects and 4% reported swelling. None of the subjects were presented with tenderness at injection site. No new safety concern is detected here. Low frequency of local reactions was reported in the 36 children aged ≥2 to <5 years, most of the reactions were mild or moderate. Pain at the injection site (28%) was the most noted local reaction. No grade 4 reaction was reported.

Few and mostly mild systemic events were reported in both age groups. Among the 24 children aged ≥6 months to <2 years, irritability (18%) was the most commonly reported event. None of the children reported fever >38.4^{o}C. Antipyretic medication was used in 8% of the subjects. Among the subjects aged ≥2-<5 years of age, fatigue (31%) was the most commonly systemic event followed by diarrhoea (6%). Most of the events were mild or moderate at severity and no grade 4 event was reported. Antipyretic or pain medication was noted among 3% of the children.

It is noted that the frequency of local and systemic events is low. The MAH suggests that the lower frequency of reactogenicity reported in this study compared to the previous study where the subjects received a

primary series of the Original 3 µg vaccine (EMEA/H/C/005735/X/0138 procedure) is a factor of the small number of participants in this study. It should however be noted that in the study presented in EMEA/H/C/005735/X/0138 procedure, the frequency of the reported systemic events was almost similar among the children that received original and placebo, suggesting that the frequency of systemic events might not be too different between original and the Original/Omicron BA.4-5 in these age groups. It is however not possible to compare between studies or to draw any firm conclusions based only on 24+36 participants. Nevertheless, the low reported frequency of both local and systemic events in this study does not suggest new or additional safety concerns in terms of reactogenicity.

AEs: Up to the cut-off date, AEs were reported by 3 (12.5%) children aged ≥6 months to <2 years and in one (2.8%) child in the 2 to <5 years of age group. No severe, life-threatening, SAE or adverse event leading to withdrawal was reported. No AESI was reported. Two of the AEs were considered related to vaccination, these were consistent with reactogenicity events (fatigue, pain at the injection site).

No new safety concern was identified among the limited number of subjects aged 6 months to <5 years receiving Original/Omicron BA.4-5 1.5/1.5 µg as a fourth dose.

C4591048 and C4591044

In these two studies, BNT162b2 Original/Omicron BA.4-5 was administered as a fourth dose at 10 µg to subjects aged ≥5 to <12 years of age, at 30 µg to subjects aged ≥12-17 years and at 30µg or 60 µg to subjects ≥18 years of age. Among the subjects that received either 30 or 60 µg, a clear trend to higher reactogenicity with higher dose was noted. No new safety concerns were identified in those studies.

2.6.7. Conclusions on clinical safety

BNT162b2 Original/Omicron BA.4-5 at 1.5/1.5 µg has been administered as a fourth dose to 60 subjects aged ≥6 months to <5 years. Overall, the reactogenicity profile was in line with the results obtained when the monovalent BNT162b2 at 3 µg was administered as a primary series. The frequency of reported AEs and SAEs was very low.

Supportive data for extrapolation purposes has been provided, where subjects in different age groups from 5 years onwards have received the bivalent vaccine at different dose levels as a fourth dose. The results suggest a similar safety profile between the monovalent original and the bivalent Original/Omicron BA.4-5 vaccine.

From a safety perspective, this suggests that the bivalent vaccine could be used as a primary series and booster for the age group ≥6 months to <5 years of age.

2.7. Risk Management Plan

The **currently valid** RMP is **version 9.0**, which was approved in procedure EMEA/H/C/005735/II/0147 on 10 November 2022 and is a consolidated EU RMP version that merges RMP v 7.2 and 8.0 and addresses the PRAC preliminary assessment request to remove Myocarditis and Pericarditis, and Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) as safety concerns in study C4591048.

Following the Renewal approval with cMA conversion to standard MA (R-0137, EC decision: 10 October 2022), C4591001 and C4591007 are re-classified from category 2 to category 3 studies.

Milestones changed for studies C4591030 and C4591048; new milestone added for protocol amendment 2 of study C4591044.

Annex 2 to include changes performed in PART III.2
Annex 3 updated to include study C4591044 in Part C.
Annex 8 updated to reflect new changes.

Within the current procedure an **updated RMP version 9.1** dated 01 March 2023 was submitted in support of:

- **EMEA/H/C/005735/X/0176** the line extension of the indication to infants and children 6 months to 4 years of age to receive bivalent Omicron BA.4-5 modified vaccine (Comirnaty Original/Omicron BA.4-5 (3 micrograms) for primary series and as a 4th dose booster.
- **EMEA/H/C/005735/II/0177/G** the variation type II of the indication to children 5 to 11 years of age and to individuals 12 years of age and older to receive bivalent Omicron BA.4-5 modified vaccine (Comirnaty Original/Omicron BA.4-5 (10 or 30 micrograms) for primary series.

2.7.1. Safety Specifications

Table SVIII.1: Summary of the Safety Concerns

Important Identified Risks	Myocarditis and Pericarditis
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

Discussion on safety specification

No new safety concerns have been identified and therefore the summary of safety concerns is similar as in previous version of the RMP.

Conclusions on the safety specification

It is agreed that the safety concerns listed by the applicant are appropriate.

2.7.2. Pharmacovigilance plan

Routine pharmacovigilance

Section *III.1 Routine pharmacovigilance* was largely unchanged relative to the approved RMP version 9.0, with the exception of the following addition (added text in green):

In the section *Potential Medication errors/Vial differentiation* the Tozinameran/Famtozinameran 1.5/1.5 mcg formulation has been added in the text as follows:

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg)/dose – 6 months through 4 years of age, Dilute before use - Maroon cap: If attempted to not dilute with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution, the user would only be able to extract approximately 1 dose instead of 10 doses as the filled volume is 0.4 mL. If 1.8 mL of diluent (purple cap amount) or 1.3 mL of diluent (orange cap amount) were used, this under dilution would also reduce the number of doses retrieved out of the vial, which might indicate to the HCP that there had been an error in preparation.

In *Table 27* Vaccine Presentation Characteristics (below) the new formulation has been added in the last column.

Table 27. Vaccine Presentation Characteristics

Age group	12 years and older				5 through 11 years		6 months through 4 years	
INN	Tozinameran	Tozinameran	Tozinameran/ Riltozinameran	Tozinameran/ Famtozinameran	Tozinameran	Tozinameran/ Famtozinameran	Tozinameran	Tozinameran/ Famtozinameran
Name	Comirnaty 30 mcg/dose DILUTE BEFORE USE Purple Cap	Comirnaty 30 mcg/dose DO NOT DILUTE Grey Cap	Comirnaty Original/Omicron BA.1 DO NOT DILUTE Grey Cap	Comirnaty Original/Omicron BA.4-5 DO NOT DILUTE Grey Cap	Comirnaty 10 mcg/dose DILUTE BEFORE USE Orange cap	Comirnaty Original/Omicron BA.4-5 DILUTE BEFORE USE Orange cap	Comirnaty 3 mcg/dose DILUTE BEFORE USE Maroon cap	Comirnaty Original/Omicron BA.4-5 DILUTE BEFORE USE Maroon cap
Dose	30 mcg (with dilution)	30 mcg (no dilution)	15/15 mcg (no dilution)	15/15 mcg (no dilution)	10 mcg (with dilution)	5/5 mcg (with dilution)	3 mcg (with dilution)	1.5/1.5 mcg (with dilution)
Vial cap color and Label with Color Border	Purple	Grey	Grey	Grey	Orange	Orange	Maroon	Maroon
Dose Volume	0.3 mL	0.3 mL	0.3 mL	0.3 mL	0.2 mL	0.2 mL	0.2 mL	0.2 mL
Amount of Diluent Needed per Vial	1.8 mL	NO DILUTION	NO DILUTION	NO DILUTION	1.3 mL	1.3 mL	2.2 mL	2.2 mL
Fill Volume	0.45 mL	2.25 mL	2.25 mL	2.25 mL	1.3 mL	1.3 mL	0.4 mL	0.4 mL
Doses per vial	6 doses per vial (after dilution)	6 doses per vial	6 doses per vial	6 doses per vial	10 doses per vial (after dilution)	10 doses per vial (after dilution)	10 doses per vial (after dilution)	10 doses per vial (after dilution)
Formulation	PBS sucrose	Tris sucrose	Tris sucrose	Tris sucrose	Tris sucrose	Tris sucrose	Tris sucrose	Tris sucrose

PBS = Phosphate Buffered Saline; Tris = Tromethamine Buffer or (HOCH2)3CNH

Summary of planned additional PhV activities from RMP

The MAH amended the following text (added text in green, deleted text in ~~strike-through~~):

The MAH proposes ~~20~~ 22 studies, of which 5 global,~~5~~ 6 in Europe only, ~~7~~ 8 in US only, 2 in US and Canada and 1 in New Zealand/Australia. There are 9 interventional studies (C4591001, C4591007, C4591015, BNT162-01 Cohort 13, C4591024, C4591031, C4591044, C4591048 and 1 study for vaccine interactions), 3 Low-Interventional studies (C4591036, WI235284 and WI255886) and ~~8~~ 10 non-interventional studies (~~7~~ 9 safety and 1 effectiveness).

Besides a few editorial changes, the RMP tables summarising *On-going and planned additional pharmacovigilance activities* remain unchanged [and are not reproduced here].

The two newly added Non-interventional studies are:

Study C4591051 is a Comirnaty Original /Omicron BA.4-5 safety surveillance study to be conducted using secondary data from administrative claims and electronic health records from data research partners participating in the US Sentinel System.

Study C4501052 is a Comirnaty Original/Omicron BA.1 and Comirnaty Original /Omicron BA.4-5 safety surveillance study conducted in collaboration with University Medical Center Utrecht on behalf of Vaccine Monitoring Collaboration for Europe Consortium research team VAC4EU and based on the master surveillance protocol.

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
C4591051 (US)	Post-approval observational studies using real-world data are needed to assess the association between COVID-19 bivalent Omicron-modified Vaccine and safety events of interest among persons administered the vaccine in the overall US population. This observational study will capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the Pfizer-BioNTech COVID-19 bivalent Omicron-modified Vaccine since its availability under an EUA using electronic health records and	Myocarditis/pericarditis Use in pregnancy Use in immunocompromised patients Long-term safety data	Planned	Protocol synopsis: 31 Jan 2023 Protocol: 31 May 2023 Final CSR: 31 Jan 2028

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	claims data from data partners participating in the Sentinel System.			
C4591052 (EU)	Post-approval observational studies using real-world data are needed to assess the association between Pfizer-BioNTech COVID-19 bivalent Omicron-modified Vaccine and safety events of interest among persons administered the vaccine in the overall EU population. This observational study will capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the COVID-19 bivalent Omicron-modified Vaccine since its availability.	Myocarditis/pericarditis Use in pregnancy 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		Protocol synopsis: 04 Jan 2023 Protocol: 30 Apr 2023 Final CSR: 31 Oct 2025

*Category 1 studies are imposed activities considered key to the benefit risk of the product.
Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Overall conclusions on the PhV Plan

Within the context of routine pharmacovigilance the MAH is expected and has committed to take into account the introduction of any (also future) new formulation(s) upon evaluation of any new unexpected trends or patterns in adverse event reporting (*e.g.* medication errors, reactogenicity, immunogenicity), as appropriate.

The full study protocol for C4591052 and C4591051 is currently ongoing.

PRAC, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.3. Plans for post-authorisation efficacy studies

Not applicable.

2.7.4. Risk minimisation measures

Routine Risk Minimisation Measures

No changes are proposed. This is accepted.

Additional risk minimisation measures

Not applicable.

Overall conclusions on risk minimisation measures

PRAC having considered the data submitted was of the opinion that:

the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Part VI Summary of the risk management plan

PRAC concludes that the updates are administrative and acceptable.

The elements for a public summary of the RMP do not require revision following the conclusion of the procedure.

2.7.5. Conclusion on the RMP

After the PRAC meeting, the MAH took the opportunity and submitted RMP version 10.0, merging versions 9.2, 9.3, and 9.4 of the RMP submitted and reviewed with this procedure, procedure X180, and II177, and implementing an agreed 6 months delay for interim report of study C4591007. The CHMP considered that the risk management plan version 10.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. 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.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. 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.

• English-only labelling (inner and outer label/carton) and package leaflet* (from start of supply until end 2023).

• Without country-specific information, such as blue box requirements (from start of supply until end 2023).

All MSs (with one exception: Poland**) have agreed to extend the current derogations until the end of 2023; this will allow the MAH to make all necessary adjustments so that by Jan 2024 the MAH can revert to full EU labelling requirements.

*MAH should ensure provision of the package leaflet in national language(s) to relevant member states, separately to vaccine supply, as stated in Q2 Q&A flexibilities for COVID-19 vaccines, with the exception of Germany.

**The MAH should address this labelling exemption request directly to the Polish NCA.:

2.9.3. Quick Response (QR) code

The updates of the QR code/URL to include further references to Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose 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).

2.9.4. 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. Introduction

This application concerns an extension of indication to add a new strength of 1.5/1.5 micrograms/dose for Comirnaty bivalent (Original/OMI BA.4-5), as primary series and booster for children 6 months-< 5 years.

There are no data investigating the bivalent BNT162b2 (Original/OMI BA.4-5) as a primary series in any age group: the evaluation is solely based on extrapolation from booster studies where the product was given as the fourth dose. There are no dose-finding studies for this age group with Original or the bivalent vaccines below the 3 µg dose.

The ETF has previously concluded that the bivalent formulation may be used for primary vaccination (https://www.ema.europa.eu/en/news/etf-concludes-bivalent-original-omicron-ba4-5-mrna-vaccines-may-be-used-primary-vaccination) based on non-clinical studies and data on the immune response following natural infection with omicron BA.4/5. The data suggested that primary vaccination with the bivalent formulation should give rise to a broad immune response in unvaccinated people and that the safety profile would be comparable to the original vaccine (based on booster studies).

In accordance with the recommendations from the EMA statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants (https://www.ema.europa.eu/en/documents/other/ecdc-ema-statement-updating-covid-19-vaccines-composition-new-sars-cov-2-virus-variants_en.pdf), the vaccine posology has been simplified for all approved formulations.

3.2. Therapeutic Context

3.2.1. Disease or condition

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human-to-human transmission.

3.2.2. Available therapies and unmet medical need

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 has been the most effective medical countermeasure to decrease the risk and mitigate spread of the SARS-CoV-2 virus.

There are COVID-19 vaccines available for the age group 6 months-< 5 years, but none specific for any Omicron variant. While the majority of the global population has either received COVID-19 vaccination or been exposed to the virus, the need for primary vaccination is considerably smaller than previously during the pandemic, however there is still demand for a vaccine that can be used for primary vaccination.

The original Comirnaty is still available, however it may be more appropriate to use variant adapted vaccines also for primary vaccination. There is currently no Omicron vaccine approved for primary vaccination in any age group.

3.2.3. Main clinical studies

To support the indication of the bivalent COVID-19 vaccine Original/Omicron BA.4-5 administered as a primary series as well as a booster dose at 1.5/1.5µg in subjects aged ≥6 months to <5 years of age, the MAH has presented data from a limited number of participants included in the study **C4591048 Substudy B Group 2 Subset ≥6 Months to <5 Years of Age**. No data where the bivalent vaccine has been administered as a primary series have been provided.

In addition, data from studies C4591048 and C4591044 including subjects ≥5 years of age and ≥12 years of age who have received the bivalent Original/Omicron BA.4-5 vaccine as a booster dose have been provided as supportive data for extrapolation purposes.

3.3. Favourable effects

Efficacy has previously been demonstrated for primary vaccination with the Original vaccine against symptomatic COVID-19 for all age groups.

Immunogenicity data of the bivalent Original/Omicron BA.4-5 as a 4th dose in children who have earlier received 3 doses of the Original vaccine were submitted. Descriptive immunogenicity data (GMTs, GMFRs, Seroresponse rate) were presented for a small subset (N= 60) of the planned study population (N=300) at age 6m-<5y.

At 1-month post, a fourth dose bivalent Original/Omi BA.4-5 at 1.5/1.5 µg in participants ⩾6 months to <5 years of age in the C4591048 Substudy B who received 3 prior doses of BNT162b2 elicited antibody responses to both BA.4-5 and the referenced strain.

The supportive data from age groups 5-<12 y (5/5 µg), and 12-17, 18-55 and >55 (15/15 µg) vaccinated with age group specific Original/Omi BA.4-5 vaccine demonstrated the immunogenicity of Original/Omi BA.4-5 as 4th dose after 3 doses of Original vaccine.

These data show that Original/Omicron BA.4-5 (1.5/1.5 µg) is immunogenic as a 4th dose in individuals older than 6m to <5 y who have received 3 prior doses of Original 3 µg. Immunogenicity studies in naïve mice showed that when compared to the original vaccine, the bivalent Omicron BA.4/BA.5 vaccine (combination of

BNT162b2 and BNT162b2 Omicron BA.4/BA.5) elicited a greater breadth of neutralizing antibody responses against all variants and sub-lineages tested.

3.4. Uncertainties and limitations about favourable effects

There are no clinical data from a primary series with a bivalent Original/Omi BA.4-5 vaccine submitted. This is valid for all age groups including children at age 6m- <5 y receiving Original/Omi BA.4-5 at 1.5/1.5 µg. The clinical data submitted for the bivalent vaccine originate exclusively from booster studies.

While the principle of extrapolation of efficacy of a bivalent booster dose to a bivalent primary series is accepted, no dose-response study has been presented for Original /Omicron BA 4-5 (1.5/1.5 µg). There were previous concerns about the immunogenicity of the total dose of 3ug in the youngest children, which has prompted a three-dose schedule. Notably, the lowest dose in the Original vaccine study was 3 µg. There are no data currently presented which could show that 1.5 µg of Original suffices to give a broad immune response that would be expected to provide protection against severe disease.

The comparison between immune responses to a fourth dose of a bivalent vaccine and a third dose of original vaccine is of less relevance, as the vaccinees have received a different number of doses. Thus, the following results would have been of interest when comparing 4th doses of both vaccines:

- Higher Omicron BA.4_5-specific neutralizing titers compared with the titers in a comparator group of participants in C4591007 Phase 2/3 who received 3 doses of Original 3 µg.
- Similar reference strain-specific titers compared with the titers in the comparator group of participants in C4591007 Phase 2/3 who received 3 doses of BNT162b2.

There is no immune correlate of protection established so far. The extent of increased efficacy given a certain increment in immunogenicity, is not known. The same pertains to the breadth of the immune response as well as the duration of protection.

The immunogenicity against newly circulating strains was shown to be low. Therefore, the clinical benefit of Original/Omicron BA. 4-5 against new strains is unknown.

3.5. Unfavourable effects

The reactogenicity profile appears to be mild among the 60 subjects aged ≥6 months to <5 years of age that received bivalent Original/Omicron BA.4-5 at 1.5/1.5 µg as a fourth dose. The most commonly reported local reaction was redness (8%) among the youngest children aged ≥6 months to <2 years of age and pain at injection site (28%) among children aged ≥2-<5 years. For systemic events irritability (18%) was most commonly reported among the youngest children and fatigue (31%) among the older children. Antipyretic or pain medication was used among 3-8% of the children.

No new safety concern was identified among the limited number of subjects aged 6 months to <5 years receiving Original/Omicron BA.4-5 at 1.5/1.5 µg as a fourth dose.

3.6. Uncertainties and limitations about unfavourable effects

The study population is limited, including only 24 participants ≥6 months <2 years of age and 36 participants ≥2 years to <5 years of age.

Safety data for BNT162b2 Original/Omicron BA.4-5 at 1.5/1.5 µg is only available when administered as a fourth dose, none of the age groups has received the bivalent vaccine as a primary series.

It is noted that the frequency of local and systemic events is low. The MAH suggests that the lower frequency of reactogenicity reported in this study compared to the previous study where subjects received a primary series of the Original 3 µg (EMEA/H/C/005735/X/0138 procedure) is a factor of the small number of participants in this study. It should however be noted that in the study presented in EMEA/H/C/005735/X/0138 procedure, the frequency of the reported systemic events was almost similar among the children that received original and placebo, suggesting that the frequency of systemic events might not be too different between original and the Original/Omicron BA.4-5 in these age groups. It is however not possible to reliably compare between studies or to draw any firm conclusions based only on 24+36 participants.

3.7. Effects Table

Table 28. Effects Table for Comirnaty Original/Omicron BA.4-5 at 1.5/1.5µg for children aged ≥6 months to <5 years of age (data cut-off: 25 Nov 2022).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Immunogenicity against Omicron BA.4-5	4th dose bivalent (1.5/1.5) µg to **6m-<5y**, after 3 doses original 3 µg	GMT (95% CI)	After 4th dose with bivalent Baseline	After 3 doses of Original 3 µg Baseline		Study C4591048 Substudy B
		Base-line	N=54 192.5 (120.4, 307.8)	N=54 70.5 (51.1, 97.2)	Small sentinel cohort from study, which intends to have larger cohort and hypothesis testing	
		1m post dose	N=58 1695.2 (1151.8, 2494.9)	N=54 607.9 (431.1, 857.2)	Minimal sample size for descriptive immunogenicity evaluation	
		GMFR (95% CI)	9.1 (6.3, 13.3)	8.6 (6.3, 11.7)	Comparator has received numerically less doses (3) than active arm (4)	
		Seroresponse rate % (95% CI)	38 out of 54 70.4 % (56.4, 82.0 %)	33 out of 54 (61.1 %) (46.9, 74.1 %)		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Immunogenicity against Omicron BA.4-5	4th dose bivalent (5/5) µg to **5-<12y**, after 3 doses original 3 µg	GMT (95% CI) 1m post dose	N= 101 1836.1 (1593.8, 2115.2)	N= 112 1632.5 (1427.5, 1867.0)	Comparator has received numerically less doses (3) than active arm (4). Model based descriptive GMR.	Study C4591048 Substudy D
		GMR	1.12 (0.92, 1.37)			
Immunogenicity against Omicron BA.4-5	4th dose bivalent (15/15) µg to **>55**, after 3 doses original 3 µg	GMT (95% CI) 1m post dose	N= 282 3373.4 (3000.3, 3793.0)	N= 273 1160.7 (1030.3, 1307.7)	Active arm and comparator have both received 4 doses	Study C4591044
		GMR	2.91 (2.45, 3.44)		Bivalent/Original among >55	Superiority met
	4th dose bivalent (15/15) µg to **>55** and **18-55** after 3 doses original 3 µg	GMT (95% CI) 1m post dose	N= 282 4344.4 (3850.2, 4902.1)	N= 294 4254.2 (3779.6, 4788.4)		
		GMR	0.98 (0.83, 1.16)		Bivalent 18-55/ bivalent >55	Non-inferiority met
Unfavourable Effects						
Redness at injection site	≥6 months to <2 years	%	Dose 4: 8%	N/A	Transient events, majority mild to moderate severity	Study C4591048 Substudy B N=24
Pain at injection site	≥2 – <5 years	%	Dose 4: 28%	N/A		Study C4591048 Substudy B N=36
Irritability	≥6 months to <2 years	%	Dose 4: 18%	N/A		Study C4591048 Substudy B N=24
Fatigue	≥2 – <5 years	%	Dose 4: 31%	N/A		Study C4591048 Substudy B N=36
Fever	≥6 months to <2 years	%	Dose 4: 4%	N/A		Study C4591048 Substudy B N=24
	≥2 – <5 years	%	Dose 4: 0%	N/A		Study C4591048 Substudy B N=36

Abbreviations: GMT: geometric mean titer; GMR: geometric mean ratio; CI: confidence interval

3.8. Benefit-risk assessment and discussion

3.8.1. Importance of favourable and unfavourable effects

The benefit of the product is the induction of an anti-SARS-CoV-2 immune response, which is likely to protect against severe COVID-19 disease. The original vaccine has proven highly effective in this regard, when used as a primary series.

Considering the following, the extrapolation of the efficacy of a bivalent original/variant vaccine from boosting to a primary series is considered in principle possible.

- Bivalent Original/Omicron BA.1 has demonstrated superior immune responses to BA.1 and non-inferior responses to the reference strain in older age groups
- Any bivalent original/variant vaccine is considered to have similar characteristics as the Original/Omicron BA.1 vaccine
- Booster responses of the same magnitude can be extrapolated to primary vaccination
- It is unknown when primary vaccination data will be available
- It is likely that primary vaccination with a vaccine covering currently circulating strains is superior against these, compared to primary vaccination with the original vaccine

As the total amount of mRNA in the bivalent vaccine is 3 µg, it is considered that the amount of mRNA is immunogenic. The ongoing Substudy A of C4591048 is investigating dose-response of Original/Omicron BA.4-5 among children younger than 5 years, data is expected to be submitted as soon as available.

The safety profiles of Comirnaty variant vaccines have not differed in a relevant way. Moreover, the reactogenicity of the selected dose in the smallest children may be considered low. Thus safety may be extrapolated from the booster scenario to the primary series.

3.8.2. Balance of benefits and risks

The benefit/risk balance is considered positive for Original/Omicron BA.4-5 at 1.5/1.5 µg among children 6m-<5y as both primary series and a booster dose

3.9. Conclusions

The overall benefit/risk balance of the bivalent BNT162b2 Original/Omicron BA.4-5 is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, immunogenicity and safety, the CHMP considers by consensus that the benefit-risk balance of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose is favourable

in the following indication:

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.

The CHMP therefore recommends the extension 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 of 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.