EMA/890789/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/005735/II/0140

Invented name: COMIRNATY

International non-proprietary name: tozinameran; tozinameran/riltozinameran

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

This application is in the area of: Quality and (Non-)Clinical RMP

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	PRAC Rapporteur Assessment Report to be circulated to CHMP, PRAC, ETF and EMA	22 Aug 2022	22 Aug 2022
☐	CHMP Rapporteur Assessment Report to be circulated to CHMP, ETF and EMA	22 Aug 2022	22 Aug 2022
☐	PRAC members comments	24 Aug 2022	24 Aug 2022
☐	CHMP members comments	24 Aug 2022	24 Aug 2022
☐	Extraordinary BWP discussion	25 Aug 2022	25 Aug 2022
☐	ETF meeting	26 Aug 2022	26 Aug 2022
☐	Updated CHMP Rapporteur Assessment Report	26 Aug 2022	26 Aug 2022
☐	PRAC plenary discussion	29 Aug 2022	29 Aug 2022
☐	Updated PRAC Rapporteur Assessment Report	30 Aug 2022	30 Aug 2022
☒	Opinion	01 Sep 2022	01 Sep 2022

List of abbreviations

Abbreviation	Definition
ADR	adverse reaction
AE	adverse event
AESI	adverse event of special interest
BLA	(US FDA) Biologics License Application
BMI	body mass index
CDC	(US) Centers for Disease Control and Prevention
COVID-19	Coronavirus Disease 2019
CSR	clinical study report
DART	developmental and reproductive toxicity
ECG	Electrocardiogram
EU	European Union
EUA	Emergency Use Authorization
FDA	(US) Food and Drug Administration
FFRNT	fluorescence focus reduction neutralization test
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	geometric mean-fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIV	human immunodeficiency virus
ICH	International Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IM	intramuscular(ly)
IND	Investigational New Drug application
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
modRNA	nucleoside-modified messenger RNA
mRNA	messenger RNA
NAAT	nucleic acid amplification testing
N-binding	SARS-CoV-2 nucleoprotein binding
P2 S	SARS-CoV-2 full-length, P2 mutant, “heads up,” prefusion spike glycoprotein
PDCO	Paediatric Committee
PIP	Paediatric Investigational Plan
PT	Preferred Term
RNA-LNP	RNA lipid nanoparticle
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
S glycoprotein, S	spike glycoprotein
SOC	System Organ Class
UK	United Kingdom
US	United States
WHO	World Health Organization

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 19 July 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
B.I.a.6.a	B.I.a.6.a - Changes to the active substance of a vaccine against human coronavirus - Replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine	Type II	I, IIIA, IIIB and A

Addition of a new strain (Omicron BA.1) resulting in a new Comirnaty bivalent Original/Omicron BA.1 (15 µg tozinameran/ 15 µg riltozinameran per dose) dispersion for injection presentation. The SmPC, the Package Leaflet and Labelling are updated accordingly. The submission includes a revised RMP version 6.0.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex A and to the Risk Management Plan (RMP).

2. Introduction

Pfizer and BioNTech have developed the COMIRNATY vaccine to prevent the 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). The COMIRNATY vaccine is also referred to as COVID-19 Vaccine (BioNTech code number BNT162b2, Pfizer code number PF-07302048).

The emergence of SARS-CoV-2 variants with multiple mutations have led Pfizer/BioNTech to develop variant vaccine constructs. Specifically, the emergence of Omicron (B.1.1.529) as a variant of concern (VOC) is the subject of this variation. To assist in the public health crisis, a new 30 µg BNT162b2 Tris/Sucrose Bivalent drug product, consisting of the original and Omicron (B.1.1.529) active substance strains, is being introduced to the MA as a new variant vaccine.

This application concerns a booster dose with a bivalent original/Omicron (BA.1) vaccine, (BNT162b2 15 µg + BNT162b2 OMI 15 µg). It is based primarily on clinical data from Study C4591031 Substudy E investigating the safety, tolerability, and immune responses in approximately 1840 older adult (>55 years of age) participants up to 1-month post-Dose 4 follow-up. Supportive data are provided from Study C4591031 Substudy D investigating safety, tolerability and effectiveness of an investigational monovalent Omicron BA.1 vaccine in approximately 640 younger adult (≥18 to ≤55 years of age) participants up to 1-month post-Dose 4 follow-up.

The Bivalent vaccine is manufactured by mixing two active substance (AS) strains in a 1:1 ratio prior to the Lipid Nanoparticle (LNP) Formation and Stabilization step and is manufactured at previously authorized/licensed Pfizer/BioNTech sites. The Bivalent vaccine is formulated in Tris/Sucrose, presented in a 30 µg total RNA dose, and filled at 2.25 mL/vial (which is intended to deliver approximately 15 µg of each strain in a 0.3 mL injection volume), allowing six doses per vial.

3. Quality aspects

3.1 Introduction

The finished product is presented as a dispersion for injection containing 15 micrograms of tozinameran and 15 micrograms of riltozinameran as active substance, embedded in lipid nanoparticles.

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

Riltozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.1).

Other ingredients are: ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159), 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), Cholesterol, Trometamol, Trometamol hydrochloride, Sucrose, Water for injections.

The product is available as a 2.25 mL dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal. Each vial contains 6 doses. Pack sizes: 10 vials or 195 vials.

3.2 Active substance (CTD module 3.2.S) - Tozinameran

The active substance tozinameran is already approved in the existing Comirnaty conditional marketing authorisation. No changes to the information related to tozinameran are proposed.

3.3 Active substance (CTD module 3.2.S) - Riltozinameran

General information (CTD module 3.2.S.1)

Section 3.2.S.1 has been updated with information related to the Omicron variant. The RNA nucleotide Sequence of the Omicron (B.1.1.529) active substance is included. It is clarified that the product codes BNT162b2 (B.1.1.529), Omicron ((B.1.1.529) and BNT162b2s05 have been used throughout the documents. It is confirmed that, except for the Omicron specific sequence, the construct is the same as for the approved variant. In general, the information provided is considered adequate. In response to a question raised by CHMP, section 3.2.S.1.3 has been updated with correct values for theoretical length and mass of the Omicron variant.

Manufacture (CTD module 3.2.S.2)

Manufacturer(s) (CTD section: S.2.1)

All proposed active substance manufacturing and testing sites are already approved in the existing Comirnaty conditional marketing authorisation (EU/1/20/1528/001-005) for the manufacture of the active substance tozinameran. The GMP compliance of these sites has been previously confirmed.

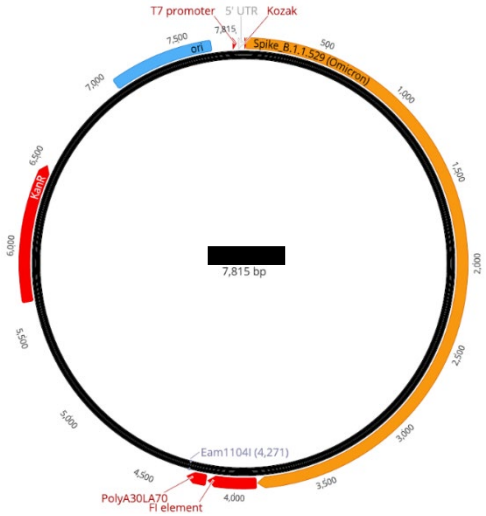
Description of manufacturing process and process controls (CTD section: S.2.2)

The manufacturing process and process controls are the same as currently approved for the manufacture of tozinameran.

Control of materials (CTD section: S.2.3)

Manufacture of the BNT162b2 Omicron (B.1.1.529) variant vaccine active substance is achieved using in vitro transcription that includes a linear DNA template as a starting material. The linear DNA template is produced via plasmid DNA from transformed DH10B Escherichia coli cells. The plasmid is a 7,815 base pair plasmid designed for the production of Omicron (B.1.1.529) variant.

Figure 3.2.S.2.3-1. Omicron Plasmid Map



BNT162b2 Omicron (B.1.1.529) variant vaccine active substance is manufactured by in vitro transcription using a linear DNA template, produced via plasmid DNA (Omicron) from transformed DH10B Escherichia coli cells. The functional elements of the Omicron plasmid are sufficiently described in graphic and tabular formats and the sequence is included. The source and generation of the Omicron plasmid are not clearly documented. However, as the plasmid used in the manufacture of the original vaccine was generated using the same procedure, included in the original dossier, and as the nucleotide differences between Omicron and the original plasmids are located only within the gene encoding the spike sequence, the information provided is considered sufficient.

The sites involved in manufacturing, testing and storage of the plasmids are listed.

The master cell bank involved in the plasmid manufacturing process is described. MCB qualification tests are listed and include morphologic and genotypic identity, DNA sequencing, absence of contaminating bacteriophages and viability. Relevant specifications are set and data from the current MCB are provided. Restriction map analysis, plasmid retention and plasmid copy number are included as characterization studies with report result as a result criterion. It is stated that any unexpected results obtained from the characterization tests will be further evaluated. The approach is endorsed.

Working cell banks (WCB) are not yet available from MCB FT1817 manufactured at Pfizer Chesterfield. Additional information has been provided on the preparation, testing and batch data for three WCBs intended to be used at Pfizer Andover GH and Hospira Zagreb, Novartis/Sandoz GmbH and AGC Biologics GmbH. Testing and characterization strategy are provided. Stability studies are also ongoing for all these WCBs batches, following a cell bank stability program, similar to the of the original plasmid WCB.

Omicron plasmid is manufactured by a fed-batch fermentation process initiated from the bacterial master cell bank, identical to the process described in the original dossier.

Specifications for the circular plasmid DNA as well as for the DNA linear template are provided. Process- and product-related impurities including host cell genomic DNA, RNA, proteins, endotoxins, bioburden and plasmid isoforms, for the plasmid DNA, are quantified routinely. Results from three different batches are provided for the circular and linearized plasmid. All analytical methods used for the control of the linear DNA template obtained from Omicron plasmid are identical to the already provided methods used for testing of the original DNA template except for the identity of the transgene region which is tested using a DNA Sanger sequencing method. This method was updated to include Omicron-specific reagents and sufficient descriptions and summary of the validation exercise are included.

A shelf life of 12 months is requested based on the BTN162b2 original vaccine and supported by limited data collected in an on-going stability study that have been initiated for the Omicron circular plasmid DNA and linearized DNA. Only 1 month data results are currently available for the specific Omicron variant. However, considering that no changes are included in the manufacturing process of the DNA template as compared to the original variant, the shelf-life is considered sufficiently supported by the original data.

Control of critical steps and intermediates (CTD section: S.2.4)

The control of critical steps and intermediates are the same as currently approved for the manufacture of tozinameran.

Process validation and/or evaluation (CTD section: S.2.5)

For process validation of the Omicron variant the Applicant refers to data on the original version of the active substance. This can be accepted since the manufacturing process is identical to that used for the original variant.

Manufacturing process development (CTD section: S.2.6)

Section 3.2.S.2.6 has been updated with a document describing manufacturing process history for the Omicron variant.

The batch numbering system is not described for the Omicron variant. In response to CHMP question, the applicant explained that the full batch numbering system was not reflected in the dossier. Each batch can be uniquely identified by material number and batch number, and the material number was previously not provided in the dossier. The batch numbers are now updated to include both the material number and the batch number. It is also described that from 01-Jul-2022 a new ERP system is used which creates unique batch numbers for each batch (across all material numbers). The dossier has been updated accordingly. The response is found acceptable.

The Applicant states that since the manufacturing process is identical to that used for the original variant and the constructs are similar, the cause and effect and the FMEA risk assessment apply to both constructs. This is agreed to.

Information on the batches manufactured to date are provided. Critical process parameters (CPPs) have been defined and in-process test for monitoring (IPT-M) and for control (IPT-C) are presented for the Omicron (B.1.1.529) active substance manufacturing process 2. The CPPs, IPT-Cs and IPT-Ms are the same as those defined for the approved variant. The acceptance criteria are in almost all cases the same as for the approved variant. This is found acceptable.

No additional comparability assessment and no process validation data is provided with this submission. For process validation of the Omicron variant the Applicant refers to data on the original version of the active substance. This can be accepted since the manufacturing process is identical to that used for the original variant. Batch analysis data provided in 3.2.S.4.4 supports consistency in manufacturing of the Omicron (B.1.1.529) variant active substance. The absence of comparability data is found acceptable since the Omicron variant constitute a new active substance. However, full characterisation of the Omicron variant should be provided, as requested in section 3.2.S.3.

Characterisation (CTD module 3.2.S.3)

In the initial submission, Section 3.2.S.3 was not updated with Omicron specific data. This was not considered acceptable, and a major objection was by raised by CHMP on the absence of characterisation data on the omicron variant, which is considered mandatory to guarantee safety of the product.

In response, the Applicant has provided characterisation data for the Omicron (BA.1) variant. The package includes confirmation of primary structure, 5'-Cap structure, higher order structure and biological activity. Essentially, the same methods as those used for characterisation of the original variant have been applied. It is noted that primary structure analysis by NGS has been excluded. However, the HPLC-UV and LC-MS/MS studies are found sufficient to confirm the primary structure.

Biological activity is confirmed by western blot analysis and cell-free in vitro translation. This is found acceptable. However, some details for the western blot analysis are lacking and the identity of the observed bands are not clear. It is recommended that the applicant provide this information post-approval.

- The expressed protein size for BNT162b2 Omicron (B.1.1.529) DS is evaluated by western blot. The Applicant claims that the protein size is consistent with the expected size of the translated protein. However, the theoretical protein sizes of the mature protein and variants thereof are not presented in the dossier. This information should be provided, and the bands observed by WB should be assigned. In addition, the antibody used for western blot should be further described, i.e., it should be stated if it targets the S1 or S2 domain of the protein. The dossier should be updated accordingly (**REC1**).

Control of active substance (CTD module 3.2.S.4)

The specification for Riltozinameran (Omicron (B.1.1.529) active substance) is presented. The active substance specifications contain tests for appearance (clarity, coloration (Ph. Eur.)), pH (Ph. Eur.), content (RNA Concentration) (UV Spectroscopy), Identity of Encoded RNA Sequence (RT-PCR), RNA Integrity (Capillary Gel Electrophoresis), 5'- Cap (RP-HPLC), Poly(A) Tail (ddPCR), Poly(A) Tail Length (IP-RP-HPLC), Residual DNA Template (qPCR), dsRNA (Immunoblot), Bacterial Endotoxin (Ph. Eur.) and Bioburden (Ph. Eur.).

The acceptance criteria are applicable from batch release to end of shelf-life. The acceptance criteria provided are based on the available data. These criteria will be reassessed and amended as appropriate when more data become available.

The proposed specification for Omicron (B.1.1.529) variant active substance follows the specification established and approved for the original variant and therefore is considered adequate.

Analytical procedures for (B.1.1.529) Omicron variant active substance (AS) release and stability testing are listed and briefly described in the dossier. Most of the analytical procedures are identical to the corresponding commercial BNT162b2 original vaccine procedures, apart from identity testing, for which Omicron variant-specific reagents are utilized. Considering that the active substance

concentration, formulation process and process control remain unchanged as compared to BNT162b2 original active substance and only a change in nucleotide sequence is differentiating the Omicron (B.1.1.529) variant, the approach is endorsed. The method is sufficiently described, and additional validation exercises have been performed at the relevant sites.

The applicant was requested to further explain and justify the claimed updates performed on the qPCR method. In response, the updates performed on the qPCR method, allowing for additional calculation which accounts for a base pair size difference between the original and the variant, have been clarified and are considered sufficiently justified.

Batch results are presented for DS batches used for clinical trials, process confirmatory studies, and stability studies. All batches met the specification acceptance criteria in place at the time of release. The specification and limits for Omicron (B.1.1.529) variant active substance is based on the BNT162b2 original active substance: Although the limited data provided for the Omicron variant are not fully supporting these limits, the strategy is found acceptable considering that only a change in the nucleotide sequence is driving the present variation. It is stated that these criteria will be reassessed and amended as appropriate when more data become available, which is endorsed.

Reference standards of materials (CTD module 3.2.S.5)

The reference standard described in Section 3.2.S.5 for the Original vaccine remains unchanged for the Omicron (B.1.1.529) variant vaccine. The Applicant was asked to sufficiently justify why a new reference standard is not considered necessary for analytical tests applied to evaluate the Omicron variant. In response, the Applicant explained that the only assay that requires a reference standard is the DP fluorescence assay. As mRNA of the Omicron (B.1.1.529) vaccine variant has the same structure, highly similar sequence, size and base composition as that of the Original vaccine variant, it is found acceptable to use the same reference standard. The justification is found acceptable.

Container closure system (CTD module 3.2.S.6)

The container closure system is the same as for the currently approved active substance, tozinameran.

Stability (CTD module 3.2.S.7)

The proposed shelf-life for the Omicron (B.1.1.529) active substance is 6 months when stored at the intended storage condition of -20 ± 5°C in EVA bags. Thus, the proposed shelf-life and storage conditions are identical to those for the original variant. The shelf-life claim is based on primary stability studies conducted on the commercial active substance batches of the original vaccine.

Stability studies for the Omicron batches are on-going. Protocols for the studies are provided. To date three months stability data for a clinical batch and one month's data for a confirmatory batch has been provided. In addition, one month's data is provided from accelerated and thermal stress studies. All data provided to date meet the acceptance criteria in place at the time of testing. This is acknowledged.

Since accurate stability protocols are provided, no trends are observed at accelerated conditions and since the original and Omicron variants are considered very similar, the claimed shelf-life is considered sufficiently justified based on data from the original variant.

3.4 Finished product (CTD module 3.2.P)

Description and composition of the finished product (CTD module 3.2.P.1)

The bivalent vaccine finished product is a preservative-free, sterile dispersion of RNA-containing lipid nanoparticles in an aqueous cryoprotectant buffer for intramuscular administration. The bivalent

finished product is formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4 and contains an approximate 1:1 ratio of the original (tozinameran) and omicron (BA.1) (riltozinameran) variant strains. The bivalent finished product is filled at 2.25 mL fill volume, is administered without dilution providing 6 doses at 30 µg RNA/dose in 0.3 mL injection volume. Each strain, original and omicron (BA.1), is present at approximately 15 µg/dose.

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

Table P.1-1. Composition of Bivalent Finished Product, 30 µg RNA dose in 0.3 mL Injection Volume, 6 Dose Multi-dose Vial

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)	Amount per 2.25 mL vial[a]	Amount per 30 µg dose
BNT162b2 (Original) drug substance	In-house specification	Active ingredient	0.05	113 µg	15 µg
BNT162b2 Omicron (B.1.1.529) drug substance	In-house specification	Active ingredient	0.05	113 µg	15 µg
ALC-0315	In-house specification	Functional lipid	1.43	3.22 mg	0.43 mg
ALC-0159	In-house specification	Functional lipid	0.18	0.41 mg	0.05 mg
DSPC	In-house specification	Structural lipid	0.31	0.70 mg	0.09 mg
Cholesterol	Ph. Eur.	Structural lipid	0.62	1.40 mg	0.19 mg
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103	231.8 mg	31 mg
Tromethamine (Tris base)[b]	USP-NF, Ph. Eur.	Buffer component	0.20	0.45 mg	0.06 mg
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)[c]	In-house specification	Buffer component	1.32	2.97 mg	0.4 mg
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.
Processing Aids/Residues[d]					
Ethanol	Ph. Eur.	Processing aid	N/A		
Citric acid monohydrate	Ph. Eur.	Processing aid			
Sodium citrate	Ph. Eur.	Processing aid			
Sodium hydroxide	Ph. Eur.	Processing aid			
HEPES	In-house specification	Drug substance buffer component			
EDTA	Ph. Eur., USP-NF	Drug substance buffer component			

| Name of Ingredients | Reference to Standard | Function | Concentration (mg/mL) | Amount per 2.25 mL vial[a] | Amount per 30 µg dose |

a. Values are rounded to maintain the same level of precision as the label claim, with trailing decimals not shown, where applicable.
b. Also known as Trometamol
c. Also known as Tromethamine HCl and Trometamol HCl
d. The processing aids and drug substance formulation buffer components are residues that are essentially removed through the manufacturing process and are not considered ingredients (excipients).
Abbreviations:
ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine
q.s. = quantum satis (as much as may suffice)
HEPES = 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
EDTA = edetate disodium dihydrate

All excipients except the functional lipids ALC-0315 and ALC-0159, the structural lipid DSPC and the buffer component TRIS HCl comply to Ph. Eur. grade. The functional lipids ALC-0315 and ALC-0159, the structural lipid DSPC and the buffer component TRIS HCl are all used in the currently approved Tris/sucrose and PBS/sucrose drug formulations of Comirnaty (EU/1/20/1528/001-005).

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 (CTD module 3.2.P.2)

This Type II-variation introduces a bivalent finished product of Comirnaty that is a preservative-free, sterile dispersion of RNA-containing lipid nanoparticles in an aqueous cryoprotectant buffer for intramuscular administration. The bivalent finished product is formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4 and contains an approximate 1:1 ratio of the original and omicron variant strains. The bivalent finished product is filled at 2.25 mL fill volume, is administered without dilution providing 6 doses at 30 µg RNA/dose in 0.3 mL injection volume. Each strain, original and omicron (BA.1), is present at approximately 15 µg/dose.

Two active substances are utilized in the bivalent vaccine, the original active substance (tozinameran) and omicron (BA.1) active substance (riltozinameran). The original and omicron active substances are combined in an approximately 1:1 ratio by mixing prior to LNP formation.

The formulation of the bivalent vaccine includes four lipids as well as some other excipients that are identical with the composition of the currently approved original vaccine of Comirnaty in the Tris/sucrose formulation (EU/1/20/1528/002-005).

A revised QTPP has been developed for the bivalent vaccine and is presented below in Table P.2-1. No changes have been made compared to the QTPP for the original vaccine in Tris/sucrose formulation except for a reflection of the use of two strains of mRNA, the inclusion of RNA ratio as a quality attribute and that the claimed shelf-life is 12 months.

Table P.2-1. Quality Target Product Profile – BNT162b2 Bivalent (Original and Omicron) Finished Product.

Product Element	Product Quality and Performance Characteristics	Quality Attributes
Efficacy		
Product Type	Vaccine based on SARS-CoV-2 S glycoprotein antigens encoded in RNA	Identity of Encoded RNA Sequence In Vitro Expression RNA Integrity 5'-Cap Poly(A) Tail
Indication	Prevention of coronavirus disease 2019 (COVID-19), which is caused by the SARS-CoV-2 viruses.	
Dosage Form	Suspension for Injection, Dispersion for Injection	
Drug Product Shelf Life[a]	-90 °C to -60 °C (12 months or more) Allows for storage at 2 to 8 °C (10 weeks or more) within the 12 months shelf life	

Product Element	Product Quality and Performance Characteristics	Quality Attributes
Formulation, Ingredients (Drug Product)	0.05 mg/mL SARS-CoV-2 S glycoprotein (Original) antigen encoding mRNA and 0.05 mg/mL SARS-CoV-2 S glycoprotein Omicron (B.1.1.529) variant antigen encoding mRNA formulated in lipid nanoparticles comprising 1.43 mg/mL ALC-0315, 0.18 mg/mL ALC-0159, 0.31 mg/mL DSPC, and 0.62 mg/mL cholesterol with 0.20 mg/mL tromethamine, 1.32 mg/mL Tris HCl, and 103 mg/mL sucrose.	Appearance (Clarity, Coloration) pH Lipid Identities LNP Size LNP Polydispersity RNA encapsulation RNA Integrity In Vitro Expression ALC-0315 Content ALC-0159 Content DSPC Content Cholesterol Content RNA Ratio
Dosage Strength	30 µg total RNA per 0.3 mL dosing solution; 6 doses per multi-dose vial.	RNA Content RNA Ratio Vial Content (volume)

Product Element	Product Quality and Performance Characteristics	Quality Attributes
Safety		
Primary Package	2 mL Type I borosilicate glass vial with 1.2 mm wall thickness, with a 13 mm bromobutyl stopper and an aluminum seal with flip-off cap OR 2 mL aluminosilicate glass vial with a 13 mm bromobutyl stopper and an aluminum seal with flip-off cap OR 2 mL Type I borosilicate glass vial with 1.0 mm wall thickness, with a 13 mm bromobutyl stopper and an aluminum seal with flip-off cap	Appearance (Visible Particulates) Subvisible Particles Bacterial Endotoxin Sterility Container Closure Integrity
Drug Product Quality Requirements	Meets pharmacopoeial requirements for parenteral dosage form as well as product-specific requirements	
Type	Preservative-free, multi-dose vial	
Size	2 mL glass vial; Six 30 µg total RNA doses doses per multi-dose vial	
Tolerability and Clinical Relevance		
Compatibility with Dosing Components	Drug is stable for duration of dosage preparation and administration	Appearance (Clarity, Coloration) pH Osmolality RNA Integrity RNA Content RNA Ratio In Vitro Expression Container Closure Integrity Vial Content (volume)
Dosing Tolerability	Acceptable (local) toleration on intramuscular injection administration	
Compatibility with Co-administered Drugs	Not planned for co-administration	

a. Target storage durations, pending additional stability data.
Abbreviations: LNP = lipid nanoparticle; ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate); ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide; DSPC = 1,2-Distearoyl-sn-glycero-3-phosphocholine

According to the applicant, no change in physicochemical properties, processability and stability is expected for the bivalent vaccine compared to the original vaccine in the Tris/sucrose formulation. This is agreed to.

A development history and lot genealogy and usage of the bivalent vaccine has been provided. An initial supportive clinical finished product lot (Pfizer Andover) and a confirmatory finished product lot (Pfizer, Puurs) has been manufactured as well as an additional lot at commercial scale (Pfizer, Puurs).

The original and bivalent finished product manufacturing processes have identical unit operations and the processing parameters for these steps are maintained. The only difference to the manufacturing processes is the DS dilution step and a confirmatory lot was manufactured to demonstrate acceptability of this step.

The LNP and finished product formulations and processes have remained the same throughout development of the original vaccine except for necessary changes to the scale as development progressed from initial clinical supplies to commercial manufacture, and changes related to the introduction of the Tris/sucrose formulation from the PBS/sucrose formulation.

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

For the bivalent vaccine, batch analysis data are provided in section 3.2.P.5.4 for the batches manufactured to date, i.e. for a commercial scale confirmatory batch and two supportive batches. All these batches met the specification acceptance criteria in place at the time of testing. This is found acceptable.

The process used to manufacture the bivalent finished product is essentially the same as the validated process used to manufacture the original vaccine in the Tris/sucrose formulation.

The bivalent finished product requires both active substances to be combined in an approximately 1:1 ratio, whereas the original vaccine uses a single active substance. Process parameters utilized for mixing the diluted active substance in the original vaccine are applied to the mixing of the diluted active substances of the bivalent vaccine and result in a homogeneous solution, as the original and omicron active substances have very similar solution properties.

Results from mixing studies and characterization data have been provided demonstrating the ability to apply the existing validated manufacturing process parameters from the original vaccine to the bivalent finished product giving a homogeneous finished product with the desired quality attributes. Two lots have been manufactured for commercial supply at Puurs, lot GA2789 which is the confirmatory lot and an additional commercial supply lot, GC3898. These lots were subject to additional characterization to confirm homogeneity of the active substances after mixing and in the finished product lot. Satisfactory results have been provided in support of the conclusions made. The overall design of these tests was the following: Upon pooling and dilution, the active substance batches (original and omicron DS batches) were mixed using the original finished product mixing process. A sample was pulled out following the mixing process to test RNA concentration and RNA ratio. After LNP manufacturing and fill and finish, samples were taken from the beginning, middle and end of the filling process and tested for RNA concentration, RNA encapsulation and RNA ratio. The provided data confirm that the bivalent process results in homogeneous mixing of both strains. Furthermore, all finished product release testing attributes were within the acceptance criteria of the finished product specifications document in section 3.2.P.5.1.

This is found acceptable.

The control strategy for bivalent finished product is based upon the control strategy for the original vaccine in the Tris/Sucrose formulation.

All quality attributes and controls described for the original vaccine in the Tris/Sucrose formulation are still applicable to the bivalent finished product. In addition, RNA Ratio is introduced as a quality attribute specific to the bivalent finished product. Furthermore, it can be noted that the weight of original and the weight of omicron active substance has been categorized as a CPP with a set-point to achieve an approximate 1:1 ratio by mass.

The analytical testing strategy for the bivalent finished product identity and RNA ratio testing uses a method based on reverse transcription droplet digital polymerase chain reaction (ddPCR). This method is described in section 3.2.P.5.2 and validation data provided in section 3.2.P.5.3. The ddPCR-method is also included in the finished product specifications document in section 3.2.P.5.1 for the use in release testing of finished product.

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.

Sufficient information has been provided in section P.2.5 with respect to microbiological attributes.

Acceptable information from compatibility studies has been provided in section P.2.6.

In conclusion, the information provided on the pharmaceutical development of the bivalent vaccine is found sufficient and acceptable.

Manufacture (CTD module 3.2.P.3)

The bivalent vaccine is manufactured at manufacturing sites, and using the same platform manufacturing process, as currently approved for Comirnaty Tris/Sucrose vaccine formulation (EU/1/20/1528/002-005). The GMP compliance of these sites has been previously confirmed.

The manufacturing process consists of LNP fabrication, bulk finished product formation, sterile filtration and aseptic filling. There are no changes in the manufacturing except for the first step including thawing and mixing of active substance. In the manufacture of the bivalent vaccine both original and omicron (BA.1) strains are combined to an approximately 1:1 ratio by mass. Similar controls during manufacturing and similar hold timed are applied for both original and bivalent finished product. The manufacturing process is considered sufficiently described including acceptable in-process controls (IPCs) and hold times.

The maximum commercial batch size is XX L of bivalent finished product solution, corresponding to approximately XX vials. A batch size range of XX – YY L may be used. The batch size range is similar to the approved original Tris/Sucrose vaccine.

No process validation is performed for the bivalent finished product. A mixing study to evaluate homogeneity is performed and data are provided. Section 3.2.P.2.3 of the dossier has been updated to provide a third commercial scale batch (GC3889) of the bivalent vaccine finished product. GC3898 was manufactured at XX L scale, while both GA2789 and GC3889 were manufactured at XX L scale. All three batches are studied at the beginning, middle and end of the filling process confirming a homogeneous mixing of both strains. This is found acceptable.

Control of excipients (CTD module 3.2.P.4)

The bivalent vaccine contains the same excipients as the currently approved Comirnaty vaccine (Tris/Sucrose formulation).

The lipid nanoparticle (LNP) consists of two functional lipids; a cationic lipid (ALC-0315) and a PEGylated lipid (ALC-0159) and two structural lipids; DSPC and cholesterol. Other excipients are sucrose, tromethamine (Tris base), Tris HCl and water. Processing aids used during manufacturing are ethanol, citric acid monohydrate, sodium hydroxide, HEPES and EDTA. All excipients are sufficiently controlled in accordance with in-house specifications and/or Ph. Eur. monographs.

Control of finished product (CTD module 3.2.P.5)

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

This comprehensive set of relevant tests with corresponding acceptance criteria and are based on those established for the original finished product for the majority of the test attributes. The acceptance criteria for release and stability testing of the bivalent finished product are the same as for the original vaccine for all quality attributes except for the RNA ratio that is related to the mixing of the original and omicron strains.

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

For the RNA ratio, a limit for the original and the omicron strains is proposed. This is not fully justified by the submitted batch data and no additional justification is provided. It is acknowledged that the experience is limited to a small number of finished product lots, manufactured from a limited number of active substance batches, and the current specifications provide adequate assurance on the ratio. Nevertheless, when a sufficient number of BNT162b2 Bivalent (Wildtype and Omicron) Finished Product batches are manufactured, the MAH has provided a commitment to reassess and optimise the proposed specification for the RNA ratio by Q2 2023 (**REC2**).

In the control of BNT162b2 Bivalent (Wildtype and Omicron) Finished Product, a droplet digital Polymerase Chain Reaction (ddPCR) method is proposed for determination of the identity of encoded RNA sequences and of the RNA ratio in the bivalent vaccine. The ddPCR technology is a digital form of polymerase chain reaction (PCR) that uses a water-in-oil emulsion system to quantify target nucleic acids. Thousands of nanoliter sized droplets are formed from each sample, and PCR amplification is then performed on each droplet. Post amplification, fluorescence is measured in order to detect the number of positive and negative droplets. It is acknowledged that ddPCR technology permits a superior quantification of low expressing/abundant targets and is less sensitive to low amounts of impurities possibly present in the reaction solution. The technical procedure is considered adequately described and the suitability of the method for the intended purpose is sufficiently justified.

The method has been validated under BTx PharmSci ARD, USA, Pfizer Global Supply (PGS) Quality Control (QC) with adequate results obtained at Grange Castle (GC), Ireland and PGS QC in Andover (AND), MA, USA. The method is therefore considered transferred to PGS GC and PGS AND through this co-validation exercise. The performance of the test method was evaluated against a set of defined acceptance criteria for an 'assay' analytical procedure (RNA ratio) and an 'identification' analytical

procedure for bivalent finished product, including precision (repeatability and reproducibility), accuracy, linearity, range and specificity. An analytical protocol detailing the validation of the analytical procedure at an additional testing laboratory, BioNTech Mainz, has been provided in the documentation. The successful completion of the analytical validation defined here will provide assurance that the analytical procedure is suitable for its intended use and is established at the additional laboratory. The approach is endorsed.

The Cell-based flow cytometry analytical procedure is used for determining in vitro expression of the SARS-CoV-2 S2 antigen in bivalent vaccine finished product transfected human embryonic kidney (HEK293T) cells. The method is identical with analytical procedure used for potency determination of the original vaccine, with the exception of the primary and secondary antibodies used in the flow cytometry analysis. To show that the method is suitable for its intended purpose, its performance was evaluated against a set of defined acceptance criteria for specificity and detection limit. Additional method characteristics including robustness, intermediate precision and reproducibility were also evaluated as part of the validation. Intermediate precision was determined for Biotherapeutics Pharmaceutical Sciences, Analytical Research and Development lab, which includes two locations (Andover and Chesterfield). Reproducibility was determined across all labs involved in the validation exercise. Based on the data provided, this method is considered validated at the laboratories that participated in the execution of the validation: BTx PharmSci ARD-BIT (Bioassay and Impurity Testing) Andover, MA, USA, BTx PharmSci ARD-BIT (Bioassay and Impurity Testing) Chesterfield, MO, USA, Pfizer Global Supply (PGS)-Quality Control (QC) in Grange Castle (GC), Ireland, PGS-QC in Andover (AND), MA, USA. and BioNTech Innovative Manufacturing Services GmbH, Idar-Oberstein, Germany.

Batch analysis data for the bivalent vaccine finished product have been provided for one confirmatory commercial scale batch (GA2789), one commercial scale batch (GC3889) and two supportive batches (22-DP-01012 - initial supportive clinical product lot (Pfizer Andover) and a confirmatory finished product lot (GC3898 – commercial scale, (Pfizer, Puurs)). All results met the acceptance criteria at the time of release. In addition, stability studies have been initiated for the supportive batch 22-DP-01012 and for the confirmatory commercial scale batch GA2789. This is found acceptable Reference standards or materials (CTD module 3.2.P.6)

The active substance reference material detailed in Section 3.2.S.5.1 is also used for the finished product. Reference material for the lipids (ALC-0315, ALC-0159, DSPC and cholesterol) is identical to the original approved Tris/Sucrose finished product. This is found acceptable.

Container closure system (CTD module 3.2.P.7)

The container closure system is the same as for the original Tris/Sucrose vaccine. No new information is provided. The bivalent vaccine is filled in type 1 borosilicate glass or aluminosilicate glass vials with bromobutyl rubber stoppers and aluminium vial seal.

Stability (CTD module 3.2.P.8)

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

The proposed shelf-life is based on the shelf-life for the original Tris/sucrose finished product, which is based on stability data obtained at the intended storage condition (-90 to -60 °C) as well as the accelerated storage conditions (-20 ± 5°C and 5 ± 3°C) during primary stability studies. Up to 2 months of stability data are available for the bivalent drug product clinical (batch 22-DP-01012) and the confirmatory batch (batch GA2789) at the intended storage condition (-90 to -60 °C) as well as at

the accelerated storage conditions (-20 ± 5°C and the 5 ± 3°C). These stability studies are currently on-going and data from these studies will be used to confirm the shelf shelf-life of the bivalent finished product. The original Tris/sucrose studies are also on-going and will be used to extend the shelf life based on the acceptability of the data.

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

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

Post-approval, a minimum of one lot of BNT162b2 Tris/Sucrose finished product will be enrolled in the commercial stability program at the long-term storage condition of -90 to -60 °C each year that finished product is manufactured.

Appendices (CTD module 3.2.A)

Not applicable.

Regional information

Not applicable.

3.5 Discussion on chemical, and 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.

3.6 Conclusions on the chemical, pharmaceutical and biological aspects

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

3.7 Recommendations for future quality development

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

1. The expressed protein size for BNT162b2 Omicron (B.1.1.529) DS is evaluated by western blot. The Applicant claims that the protein size is consistent with the expected size of the translated protein. However, the theoretical protein sizes of the mature protein and variants thereof are

not presented in the dossier. This information should be provided, and the bands observed by WB should be assigned. In addition, the antibody used for western blot should be further described, i.e., it should be stated if it targets the S1 or S2 domain of the protein. The dossier should be updated accordingly.

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

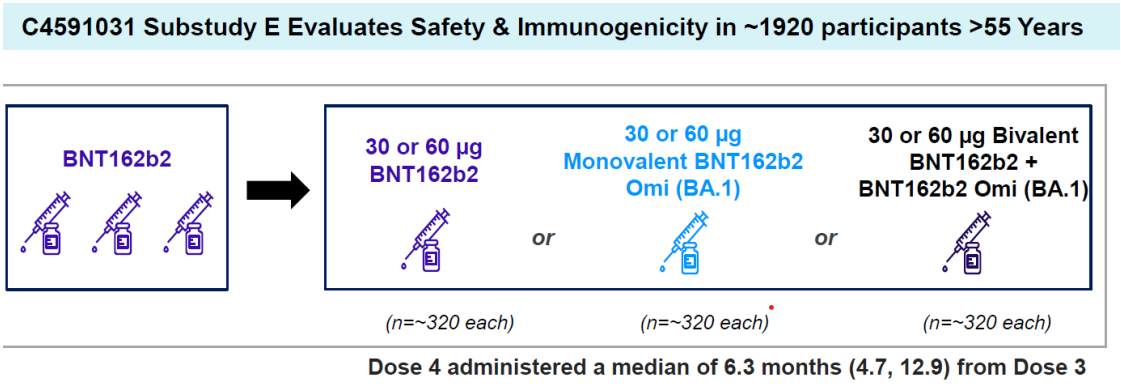
4. Clinical Efficacy aspects

Phase 1/2/3 Study C4591001 is the pivotal study for the approval of the BNT162b2 vaccine against COVID-19 in healthy individuals ≥12 years of age. The study was initiated in April 2020 and has been amended several times since then. Study C4591031 was designed to evaluate BNT162b2 boosting strategies across different populations of participants (e.g., age groups) included in the C4591001 study. The study is divided in several sub-studies.

In Substudy D, the BNT162b2 OMI dose was 30 µg, i.e. the same dose as for the initially approved monovalent vaccine (original strain). A higher dose (60 µg) of the vaccine was also evaluated in C4591031 Substudy E. The bivalent formulation was tested in two different doses: Original/Omicron BA.1 15/15 µg or 30/30 µg of each variant.

The present submission provides new clinical data in approximately 1840 participants **>55** years of age from the ongoing Study C4591031 Substudy E (BNT162b2-experienced participants), including safety and immunogenicity data up to 1 month after receipt of a single dose (Dose 4) of Original (30 µg or 60 µg), monovalent Omicron BA.1 (30 µg or 60 µg), or bivalent Original/Omicron BA.1 (15/15 µg or 30/30 µg), as described in the figure below.

Fig. Design of the Substudy E



The present submission also includes clinical data from approximately 640 participants **≥18 to ≤55** years of age from the ongoing Study C4591031, Substudy D (Cohort 2: BNT162b2-experienced participants), including safety and immunogenicity to 1 month after receipt of an additional booster (fourth) dose of an Omicron variant specific vaccine, BNT162b2 OMI 30-µg, see figure below.
A summary of the study C4591031 contributing key clinical data is provided in Table1.

Fig. Design of substudy D

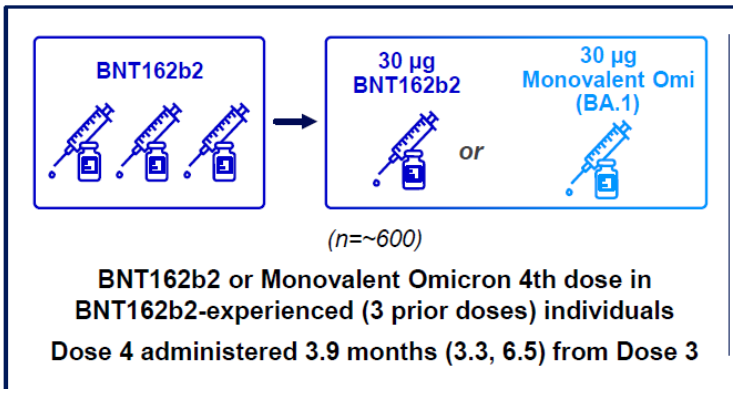


Table 1. Summary of Clinical Studies

Sponsor (Agent)	Study Number (Status)	Phase/Study Design	Test Product (Dose)	Number of Subjects	Type of Subjects (Age)
BioNTech (Pfizer)	C4591031 Substudy E (ongoing)	Phase 3, randomized, observer-blind	Expanded Cohort: Participants >55 Years G1:BNT162b2 (30 µg) G2:BNT162b2 (60 µg) G3:BNT162b2 OMI (30 µg) G4:BNT162b2 OMI (60 µg) **G5:**BNT162b2 **+** BNT162b2 **OMI (30 µg)** G6:BNT162b2 + BNT162b2 OMI (60 µg)	~1840 randomized 1:1:1:1:1:1 to receive 4th dose of BNT162b2 (30 or 60 µg) or BNT162b2 OMI (30 or 60 µg) or BNT162b2 + BNT162b2 OMI (30 or 60 µg)	Adults >55 years of age
BioNTech (Pfizer)	C4591031 Substudy D (ongoing)	Phase 3, randomized, observer-blind	Cohort 2: G1:BNT162b2 (30-µg) G2:BNT162b2 OMI (30-µg)	~640 randomized 1:1 to receive 4th dose of BNT162b2 or BNT162b2 OMI	Adults (≥18 to ≤55 years)

Note: study information relevant to the scope of data presented in the clinical overview are summarized in the table. G- group nr. BNT162b2- Original; BNT162b2 OMI- Omicron BA.1

Additional descriptive analyses from Substudy E were performed to further characterize BA.4/BA.5 neutralization responses following a booster (fourth) dose of the bivalent Original/Omicron BA.1 15/15 µg compared to the authorised vaccine (Original 30 µg). An unvalidated fluorescent focus reduction neutralization test (FFRNT) was used to determine Omicron BA.4/BA.5-specific neutralizing titers among BNT162b2-experienced adults >55 years of age who received a booster (Dose 4) of either Original 30 µg or bivalent Original/Omicron BA.1 15/15 µg in C4591031 Substudy E (Expanded Cohort).

A total of 100 participants (20 participants with baseline SARS-CoV-2 positive status and 80 participants with baseline SARS-CoV-2 negative status) were randomly selected from each vaccine group in the expanded cohort for the evaluable immunogenicity population Omicron BA.4/BA.5 neutralization assay subset.

The CHMP noted that the Novel SARS-CoV-2 human serological assay (the 384-well SARS-CoV-2 microneutralisation) was utilised in support of the current application. This is based on real virus neutralisation and therefore suitable to detect the neutralising antibodies providing protection from SARS-CoV-2 infection, as confirmed by CHMP. The assay demonstrated dilutional linearity and precision that met predefined acceptance criteria. Samples with titers greater than the ULOQ may be pre-diluted in assay buffer before testing to yield titers within the validated assay range. The performance of the assay near the LOD is acceptable to the CHMP. The correlation with earlier method 96-well SARS-CoV-2 mNeonGreen virus microneutralisation assay was demonstrated by testing. The WHO IS detection was demonstrated. Assay specificity was investigated by using non-related RSV-F protein which is acceptable to the CHMP in current settings. Assay sensitivity was ensured by testing samples with a wide range of antibody titres, long dilution series and established the LLOQ. The results documented in the revalidation report for the 384-well SARS-CoV-2 NT for the Wuhan and B1.1.529 (Omicron) Variant supports that the assay is validated and suitable for its intended use in testing clinical, epidemiological, and non-clinical study samples, as endorsed by the CHMP.

4.1 Study C4591031 Substudy E

4.1.1 Methods

Conduct of the study

C4591031 Protocol Amendment 9 was the effective protocol version at the time of the data cutoff and data analyses included in this Substudy E interim report. Protocol Amendment 9 was approved on 03 May 2022.

Study participants

This is a randomized, observer-blinded substudy of boosting study C4591031 to evaluate the safety, tolerability, and immunogenicity of standard (30 µg) and high-dose (60 µg) BNT162b2 and BNT162b2 OMI as well as a combination of the two (at 15 or 30 µg each for a total mRNA amount of 30 or 60 µg), given as a single booster dose. Approximately 1920 participants >55 years of age and 990 participants 18 to 55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 5 to 12 months prior to randomization, were enrolled at investigator sites in the US only. Participants >55 years of age were randomized at a ratio of 1:1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 OMI at 30 µg, BNT162b2 OMI at 60 µg, a combination of BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), or a combination of BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each) at Visit 601 as a fourth dose.

Participants must have met all of the general inclusion and exclusion criteria as specified for the master protocol and the Substudy E-specific criteria. All participants were centrally assigned to randomized study intervention using an IRT.

Study E Immunogenicity Objectives, Estimands and Endpoints

The data presented in this interim CSR are shown for the objectives/endpoints in Table 2. Those to be reported later are not included here.

Note: Omicron with no specification refers to Omicron BA.1, unless otherwise specified.

Table 2. Substudy E objectives, estimands and endpoints relevant to current application

Primary Immunogenicity		
Objectives	**Estimands**	**Endpoints**
G3vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI 30 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-	• SARS-CoV-2 Omicron-neutralizing titers

	experienced participants	
G4vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of BNT162b2 OMI 60 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron-neutralizing titers
G5vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of **bivalent** BNT162b2 and BNT162b2 OMI at **30 µg** compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2- experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron-neutralizing titers

G6vG1A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of anti-Omicron immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2- experienced participants • The difference in percentages of participants with seroresponse[a] to the Omicron strain at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg and at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron-neutralizing titers
Secondary Immunogenicity		
G5vG1B: To demonstrate the noninferiority of anti-reference-strain immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the reference strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 30 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 reference strain–neutralizing titers
G6vG1B: To demonstrate the noninferiority of anti–reference strain immune response after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2- experienced participants >55 years of age	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention given as a fourth dose) of past SARS-CoV-2 infection: • GMR of the reference strain–neutralizing titers at 1 month after 1 dose of bivalent BNT162b2 and BNT162b2 OMI at 60 µg to those at 1 month after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants	• SARS-CoV-2 reference strain–neutralizing titers
To demonstrate the "super" superiority of anti-Omicron immune responses after 1 dose of BNT162b2 OMI at 30 µg (G3vG1B), BNT162b2 OMI at 60 µg (G4vG1B), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (G5vG1C), or bivalent BNT162b2 and BNT162b2 OMI at 60 µg (G6vG1C) compared to after 1 dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age	• Same as GMR estimands of G3vG1A, G4vG1A, G5vG1A, G6vG1A	• SARS-CoV-2 Omicron-neutralizing titers

Exploratory		
To describe the immune response to BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose in BNT162b2- experienced participants >55 years of age	• GMT at each time point • GMFRs from before the study vaccination to subsequent time points • Percentages of participants with seroresponse [a] at each time point	• SARS-CoV-2 Omicron-neutralizing titers • SARS-CoV-2 reference strain–neutralizing titers
To describe the immune response to the reference strain and VOCs for participants [c] in sentinel cohorts of each age group		• SARS-CoV-2 neutralizing titers for the reference strain and VOCs
To describe the immune response to any VOCs not already specified in each age group		• SARS-CoV-2 neutralizing titers for any VOCs not already specified
To describe confirmed COVID-19 and severe COVID-19 cases in each age group		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases

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

b) A subset of participants from Substudy D Cohort 2 that have received BNT162b2 30 µg as a fourth dose will be randomly selected for this objective.

c) This subset of participants will not contribute to the assessment of primary immunogenicity objectives.

Note: G1: BNT162b2 (30 µg); G2: BNT162b2 (60 µg); G3: BNT162b2 OMI (30 µg); G4: BNT162b2 OMI (60 µg); G5: BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (Total 30 µg); G6: BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (Total 60 µg)

Blinding

Study staff receiving, storing, dispensing, preparing, and administering the study interventions were unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, were blinded to study intervention assignments. In particular, the individuals who evaluated participant safety were blinded.

The study intervention was to be administered in such a way as to ensure that the participants remain blinded.

The sponsor (BioNTech) and sponsor agent (Pfizer Inc.) were unblinded to the study intervention allocation for the sentinel cohorts. For the expanded-enrolment part of the study, the majority of sponsor/Pfizer staff were blinded to study intervention allocation. All laboratory testing personnel performing serology assays remained blinded to study intervention assigned/received throughout the study.

Immunogenicity

Immunogenicity results for expanded cohort analyses were based on validated assays for 50% SARS-CoV-2 neutralizing titers on a newly developed 384-well assay platform (reference strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.1) at before first study (Dose 4) vaccination and 1 month after study vaccination (Dose 4) with BNT162b2, BNT162b2 OMI or BNT162b2 + BNT162b2 OMI reported as GMTs, GMRs, percentages/difference in percentages with seroresponse, GMFRs. The neutralizing titers between the 384-well platform and 96-well platform are not comparable.

A non-validated assay (FFRNT) was used to obtain SARS-CoV-2 serum neutralization titers against wider range of Omicron variants (BA.1, BA.2, BA.2.12.1, and BA.4/BA.5) in sentinel cohort and against Omicron BA4/BA5 strain from participants in the special immunogenicity subset, before study vaccination (Dose 4) and at 1-month post-Dose. The FFRNT is similar to the 50% plaque-reduction neutralization test (PRNT) assay which has been used to generate confirmatory data against the reference strain and other variants. The FFRNT assay has higher throughput and correlates well with the PRNT assay.

Sample size

The sample size in each group is based on consideration of an acceptable safety database. For the >55-year age group, a random sample of 230 participants will be selected from each group in the expanded-enrolment cohort as an immunogenicity subset to evaluate the primary and secondary immunogenicity objectives. Assuming a 35% non-evaluable or prior infection rate, approximately 150 evaluable participants in each group will contribute to the primary immunogenicity evaluation.

Superiority and Noninferiority of Anti-Omicron Immunogenicity Objectives
For comparisons based on GMR, assuming common assay standard deviations of 1.05 in log scale based on data observed in the Phase 2 part of the C4591001 study for participants 56 years of age or older and adjusted for assay variability, if the true GMR is 1.5, with 150 evaluable participants, the study will have 91.5% power to demonstrate superiority. If the true GMR is 2.0, the study will have 65.7% power to declare "super" superiority using a 1.5-fold margin.

For comparisons based on seroresponse rate difference, if the seroresponse rate is 70% in the BNT162b2 OMI (30 µg or 60 µg) or bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) group and 55% in the BNT162b2 30 µg group, the study will have 94.9% power to demonstrate noninferiority using a 5% margin.

Noninferiority of Anti–Reference Strain Immunogenicity Objectives
For comparisons based on GMR, common assay standard deviations of 1.05 and a GMR of 1 are assumed for each comparison. With 150 evaluable participants and the stated assumptions for the GMR and standard deviation, the study has 90.9% power to demonstrate noninferiority based on the GMR using a 1.5-fold margin.

Immunogenicity Endpoints and analysis methods

Immunogenicity analyses were conducted based on the evaluable and all-available immunogenicity populations. Immunogenicity results were based on validated assays for 50% SARS-CoV-2 neutralizing titers against Omicron BA.1 and the reference strain from before study vaccination (Dose 4) to 1 month after Dose of BNT162b2 (30 µg or 60 µg) BNT162b2 OMI (30 µg or 60 µg) or BNT162b2 + BNT162b2 OMI (30 µg or 60 µg), reported as:

- Geometric mean titers (GMTs)
- Geometric mean ratio (GMR) of GMTs
- Percentages/difference in percentages with seroresponse
- Geometric mean-fold rises (GMFRs) in titers

The primary immunogenicity objectives were to evaluate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rates of the anti-Omicron BA.1 immune response induced by a dose of BNT162b2 OMI (30 µg or 60 µg) or bivalent BNT162b2 + BNT162b2 OMI (30 µg or 60 µg) relative to the anti-Omicron BA.1 immune response elicited by a dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age.

The primary immunogenicity analysis included individuals without serological or virological evidence of past SARS CoV 2 infection up to 1 month after study vaccination (Dose 4).

Statistical methods

Superiority and Noninferiority of Anti-Omicron BA.1 Immune Responses Analyses:

GMR: The primary analysis approach for GMR was unadjusted GMR calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided 95% CIs were obtained by calculating CIs using Student's t-distribution for the mean difference on the logarithmically transformed assay results and exponentiating the confidence limits.

As sensitivity approach, the model-based GMR and associated 95% CI was 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 with terms of baseline assay results (log scale) and vaccine group.

Simple superiority with respect to level of neutralizing titer of anti-Omicron BA.1 immune response would be declared if the lower limit of the 2-sided 95% CI for the GMR is >1 and "super" superiority for GMR would be established if the lower limit of the 2-sided 95% CI for the GMR is >1.5, after adjustment for multiplicity.

Seroresponse: defined as achieving a ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement was below the LLOQ, the postvaccination measure of ≥4 × LLOQ was considered seroresponse. The exact 95% CI for percentage of participants with seroresponse for each vaccine group was computed using the F distribution (Clopper-Pearson method). The primary approach to calculate difference in percentages and the associated 2 sided 95% CI was using the Miettinen and Nurminen method.

As sensitivity approach, the difference in seroresponse rate between 2 vaccine groups and the associated 95% CI was calculated using Miettinen and Nurminen method stratified by baseline assay result category (<median, ≥median).

Noninferiority with respect to seroresponse rate of the anti-Omicron BA.1 immune response would be declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%, after adjustment for multiplicity.

Noninferiority of Anti–Reference Strain Immune Responses Analyses:

The secondary immunogenicity objectives on anti–reference strain immune responses were to assess the noninferiority of the anti–reference strain immune response induced by a dose of bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) relative to the anti–reference strain immune response elicited by a dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2-experienced participants >55 years of age.

Noninferiority of anti-reference strain immune response will be declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8, after adjustment for multiplicity.

Additional Analyses:

GMT: calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits.

GMFR: calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

Subgroup analyses of immunogenicity were conducted based on demographic characteristics (age group, sex, race, ethnicity) and SARS-CoV-2 baseline status (positive or negative).

Analysis sets:

Enrolled: All participants who have a signed ICD.

Randomized/assigned: All participants who are assigned a randomization number in the IWR system.

Evaluable Immunogenicity: All eligible randomized/assigned participants who receive the study intervention to which they are randomized or assigned, have a valid and determinate immunogenicity result from the blood sample collected within 28-42 days after the study vaccination, and have no other important protocol deviations as determined by the clinician.

All-available immunogenicity: All randomized/assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.

Safety: All participants who receive the study intervention.

Multiplicity Adjustment

Multiple primary and secondary immunogenicity objectives in this study are being assessed in a sequential order as listed below using a 1-sided alpha of 0.025. Comparisons are made with the reference vaccine BNT162b2 30 µg.

- Superiority in GMR and noninferiority in seroresponse rate for Omicron response: G4vG1A (OMI-60) vs. reference vaccine → G6vG1A (bivalent-60) vs. reference vaccine → G5vG1A (bivalent-30) vs. reference vaccine →
- Noninferiority in GMR for reference strain response: G6vG1B (bivalent-60) vs. reference vaccine → G5vG1B (bivalent-30) vs. reference vaccine →
- "Super" superiority in GMR for Omicron response: G4vG1B (OMI-60) vs. reference vaccine → G6vG1C (bivalent-60) vs. reference vaccine → G5vG1C (bivalent-30) vs. reference vaccine →
- Superiority in GMR and noninferiority in seroresponse rate for Omicron response: G3vG1A (OMI-30) vs. reference vaccine → G3vG1B (OMI-30) vs. reference vaccine

For objectives involving 2 hypotheses, hypotheses based on GMR and seroresponse rate difference are assessed sequentially in the order as stated. Both hypotheses within the objective must be established before assessing the next objective in the sequence. Therefore, the overall type I error is fully controlled.

4.1.2 Results

Immunogenicity Population Characteristics – C4591031 Substudy E (Expanded Cohort)

A random sample of 230 participants selected from each group in the expanded-enrolment cohort constituted the immunogenicity subset to evaluate the primary and secondary immunogenicity objectives (Table 3).

Table 3. Immunogenicity Populations – Expended Cohort – Immunogenicity Subset – Participants>55 Years Age

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) n[a] (%)	BNT162b2 (60 µg) n[a] (%)	BNT162b2 OMI (30 µg) n[a] (%)	BNT162b2 OMI (60 µg) n[a] (%)	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) n[a] (%)	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) n[a] (%)	Total n[a] (%)
Randomized[b]	230 (100.0)	230 (100.0)	230 (100.0)	230 (100.0)	230 (100.0)	230 (100.0)	1380 (100.0)
All-available immunogenicity population	225 (97.8)	225 (97.8)	228 (99.1)	224 (97.4)	225 (97.8)	223 (97.0)	1350 (97.8)
Excluded from all-available immunogenicity population	5 (2.2)	5 (2.2)	2 (0.9)	6 (2.6)	5 (2.2)	7 (3.0)	30 (2.2)
Reason for exclusion							
Did not have at least 1 valid and determinate immunogenicity result after the study vaccination	5 (2.2)	5 (2.2)	2 (0.9)	5 (2.2)	5 (2.2)	7 (3.0)	29 (2.1)
Did not provide informed consent	0	0	0	1 (0.4)	0	0	1 (<0.1)
Evaluable immunogenicity population	221 (96.1)	220 (95.7)	223 (97.0)	219 (95.2)	216 (93.9)	217 (94.3)	1316 (95.4)
Participants without evidence of infection up to 1 month after the study vaccination[c]	182 (79.1)	198 (86.1)	180 (78.3)	185 (80.4)	186 (80.9)	181 (78.7)	1112 (80.6)
Excluded from evaluable immunogenicity population	9 (3.9)	10 (4.3)	7 (3.0)	11 (4.8)	14 (6.1)	13 (5.7)	64 (4.6)
Reason for exclusion[d]							
Did not meet eligibility and randomization criteria	0	0	1 (0.4)	4 (1.7)	0	1 (0.4)	6 (0.4)
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after the study vaccination	9 (3.9)	10 (4.3)	6 (2.6)	8 (3.5)	11 (4.8)	10 (4.3)	54 (3.9)
Had other important protocol deviation	0	0	0	2 (0.9)	3 (1.3)	2 (0.9)	7 (0.5)
Did not provide informed consent	0	0	0	1 (0.4)	0	0	1 (<0.1)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. n = Number of participants with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
c. Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
d. Participants may have been excluded for more than 1 reason.
PFIZER CONFIDENTIAL SDTM Creation: 27MAY2022 (12:48) Source Data: adsl Table Generation: 12JUL2022 (22:58)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2 ube/C4591031 E 1MINEXP EUA/adva s008 exp 1m

Demographic and Other Baseline Characteristics

Overall, most participants in the expanded cohort safety population were White (86.6%), with 5.5% Asian participants, 6.3% Black or African American participants, and other racial groups comprising ≤1.1% each. There were 14.9% Hispanic/Latino participants.

The median age at the time of study vaccination was 67.0 years, and 49.5% of participants were male.

Obese participants made up 35.6% of the expanded cohort. In total, 232 (12.6%) participants had baseline positive status for evidence of prior infection with SARS-CoV-2. The median time from the first booster dose of BNT162b2 (received prior to the study C4591031 Substudy E) was 6.3 months.

Demographic characteristics for the expanded cohort immunogenicity populations (evaluable immunogenicity and all-available immunogenicity population) were generally similar to those observed for the safety population and presented in the following table:

Table 4. Demographic Characteristics – Participants Without Evidence of Infection Prior to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N^a=182) n^b (%)	BNT162b2 (60 µg) (N^a=198) n^b (%)	BNT162b2 OMI (30 µg) (N^a=180) n^b (%)	BNT162b2 OMI (60 µg) (N^a=185) n^b (%)	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N^a=186) n^b (%)	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N^a=181) n^b (%)	Total (N^a=1112) n^b (%)
Sex							
Male	78 (42.9)	91 (46.0)	89 (49.4)	91 (49.2)	90 (48.4)	84 (46.4)	523 (47.0)
Female	104 (57.1)	107 (54.0)	91 (50.6)	94 (50.8)	96 (51.6)	97 (53.6)	589 (53.0)
Race							
White	157 (86.3)	168 (84.8)	155 (86.1)	162 (87.6)	173 (93.0)	162 (89.5)	977 (87.9)
Black or African American	11 (6.0)	14 (7.1)	12 (6.7)	11 (5.9)	4 (2.2)	6 (3.3)	58 (5.2)
American Indian or Alaska Native	0	0	0	1 (0.5)	0	0	1 (<0.1)
Asian	10 (5.5)	12 (6.1)	9 (5.0)	9 (4.9)	8 (4.3)	11 (6.1)	59 (5.3)
Native Hawaiian or other Pacific Islander	1 (0.5)	0	0	0	0	0	1 (<0.1)
Multiracial	3 (1.6)	4 (2.0)	4 (2.2)	2 (1.1)	0	1 (0.6)	14 (1.3)
Not reported	0	0	0	0	1 (0.5)	1 (0.6)	2 (0.2)
Ethnicity							
Hispanic/Latino	25 (13.7)	17 (8.6)	15 (8.3)	17 (9.2)	20 (10.8)	21 (11.6)	115 (10.3)
Non-Hispanic/non-Latino	157 (86.3)	181 (91.4)	165 (91.7)	168 (90.8)	166 (89.2)	160 (88.4)	997 (89.7)
Age at vaccination (years)							
Mean (SD)	66.8 (6.84)	66.8 (6.90)	67.1 (6.45)	67.0 (6.64)	67.6 (6.46)	68.0 (6.82)	67.2 (6.69)
Median	67.0	66.0	67.0	67.0	67.5	68.0	67.0
Min, max	(56, 87)	(56, 84)	(56, 84)	(56, 87)	(56, 85)	(56, 87)	(56, 87)
Time (months) from Dose 3 of BNT162b2 (received prior to the study) to the study vaccination							
n	182	198	180	185	186	181	1112
Mean (SD)	6.8 (1.31)	6.8 (1.45)	6.9 (1.41)	6.9 (1.50)	6.7 (1.30)	6.9 (1.40)	6.8 (1.40)
Median	6.3	6.3	6.3	6.3	6.3	6.3	6.3
Min, max	(5.4, 11.1)	(5.3, 12.9)	(5.4, 11.4)	(5.4, 11.6)	(4.7, 11.5)	(5.3, 11.1)	(4.7, 12.9)
<5 Months	0	0	0	0	1 (0.5)	0	1 (<0.1)
≥5 to <7 Months	141 (77.5)	152 (76.8)	130 (72.2)	136 (73.5)	143 (76.9)	134 (74.0)	836 (75.2)
≥7 to <9 Months	28 (15.4)	28 (14.1)	33 (18.3)	29 (15.7)	27 (14.5)	30 (16.6)	175 (15.7)
≥9 to <11 Months	12 (6.6)	13 (6.6)	14 (7.8)	17 (9.2)	13 (7.0)	13 (7.2)	82 (7.4)
≥11 to <12 Months	1 (0.5)	4 (2.0)	3 (1.7)	3 (1.6)	2 (1.1)	4 (2.2)	17 (1.5)
≥12 Months	0	1 (0.5)	0	0	0	0	1 (<0.1)
Body mass index (BMI)							
Underweight (<18.5 kg/m^2)	4 (2.2)	4 (2.0)	0	3 (1.6)	1 (0.5)	3 (1.7)	15 (1.3)
Normal weight (≥18.5-24.9 kg/m^2)	57 (31.3)	57 (28.8)	54 (30.0)	49 (26.5)	43 (23.1)	54 (29.8)	314 (28.2)
Overweight (≥25.0-29.9 kg/m^2)	58 (31.9)	55 (27.8)	70 (38.9)	76 (41.1)	77 (41.4)	63 (34.8)	399 (35.9)
Obese (≥30.0 kg/m^2)	63 (34.6)	82 (41.4)	56 (31.1)	57 (30.8)	65 (34.9)	61 (33.7)	384 (34.5)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
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(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2_ube/C4591031_E_1MINEXP_EUA/adsl_s005_exp_1m_cf

Extended cohort to study responses to Omicron strain BA.4/BA.5

A total of 100 participants (20 participants with baseline SARS-CoV-2 positive status and 80 participants with baseline SARS-CoV-2 negative status) were randomly selected from each vaccine group in the expanded cohort for the evaluable immunogenicity population Omicron BA.4/BA.5 neutralization assay subset. Demographic characteristics for participants in this subset were similar between the two vaccine groups.

Immunogenicity Population- Sentinel cohort

In total, all 120 participants >55 years of age in the sentinel cohort were randomized, received vaccination, and completed the 1-month post-vaccination visit. No participant in the sentinel cohort withdrew from the study. The median time from the first booster dose of BNT162b2 (received prior to the study C4591031 Substudy E) was 8.0 months.

Demographic characteristics for the sentinel cohort immunogenicity populations (evaluable immunogenicity and all-available immunogenicity population) were generally similar to those observed for the safety population.

Immunogenicity Analyses: Expanded Cohort – Participants >55 Years of Age

Superiority and Noninferiority Objectives of Anti-Omicron BA.1 Immune Responses

The primary immunogenicity objectives were to assess the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response induced by a dose of BNT162b2 OMI (30 µg or 60 µg) or bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) relative to the anti-Omicron immune response elicited by a dose of BNT162b2 at 30 µg given as a fourth dose in BNT162b2- experienced participants >55 years of age.

GMR of Omicron BA.1 Neutralizing Titers

In the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination, GMRs for the BNT162b2 OMI 30 µg group and BNT162b2 OMI 60 µg to BNT162b2 30 µg group (GMR) was 2.23 (2-sided 95% CI: 1.65, 3.00) and 3.15 (2-sided 95% CI: 2.38, 4.16), respectively (Table 12).

GMRs for the two bivalent vaccine groups BNT162b2 + BNT162b2 OMI 30 µg and BNT162b2 + BNT162b2 OMI 60 µg to BNT162b2 30 µg group was 1.56 (2-sided 95% CI: 1.17, 2.08) and 1.97 (2-sided 95% CI: 1.45, 2.68), respectively (Table 5).

Table 5. Geometric Mean Ratios For Between Vaccine Group Comparison – Participants without evidence of infection up to 1 month after the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants>55 years of Age – Evaluable Immunogenicity Population

Assay	Vaccine Group (as Randomized)	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	BNT162b2 (30 µg)	1 Month	163	455.8 (365.9, 567.6)	
	BNT162b2 OMI (30 µg)	1 Month	169	1014.5 (825.6, 1246.7)	2.23 (1.65, 3.00)
	BNT162b2 OMI (60 µg)	1 Month	174	1435.2 (1208.1, 1704.8)	3.15 (2.38, 4.16)
	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)	1 Month	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)
	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)	1 Month	175	900.1 (726.3, 1115.6)	1.97 (1.45, 2.68)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	BNT162b2 (30 µg)	1 Month	182	5998.1 (5223.6, 6887.4)	
	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)	1 Month	186	5933.2 (5188.2, 6785.2)	0.99 (0.82, 1.20)
	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)	1 Month	180	7816.9 (6820.7, 8958.6)	1.30 (1.07, 1.58)

Abbreviations: GMR = geometric mean ratio; 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: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
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. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (vaccine group in the corresponding row - BNT162b2 [30 µg]) and the corresponding CI (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 12JUL2022 (18:57) Source Data: adva Table Generation: 12JUL2022 (23:07)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2 ube/C4591031 E 1MINEXP EUA/adva s004 exp awo 1m

GMRs from the sensitivity analysis using linear regression model with terms of baseline assay results (log scale) and vaccine group are similar to the unadjusted GMR. GMR reported in the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination was similar.

Simple superiority of BNT162b2 OMI 60 µg, bivalent BNT162b2 + BNT162b2 OMI 60 µg, and bivalent BNT162b2 + BNT162b2 OMI 15+15 µg to BNT162b2 30 µg (reference vaccine) were met, as the lower bound of the 2-sided 95% CI for GMR was >1 for each of the three comparisons.

As the lower bound of the 2-sided 95% CI for GMR was >1.5, "super" superiority of BNT162b2 OMI 60 µg to BNT162b2 30 µg for the Omicron variant was achieved based on the prespecified criterion.

The lower bound of the 2-sided 95% CI for GMR was <1.5, therefore, "super" superiority of BNT162b2 + BNT162b2 OMI 30 µg and BNT162b2 + BNT162b2 OMI 60 µg to BNT162b2 30 µg for the Omicron variant was not achieved.

Hypotheses for monovalent BNT162b2 OMI 30 µg were to be tested sequentially after "super" superiority of bivalent vaccine groups. Since "super" superiority of bivalent vaccine groups was not achieved, all hypotheses (superiority in GMR and noninferiority in seroresponse rate for Omicron response) for BNT162b2 OMI 30 µg cannot be formally tested. Although not formally claimed due to multiplicity, monovalent Omicron-modified vaccine BNT162b2 OMI 30 µg also had GMR and lower bound of 95% CI (>1.5) consistent with super superiority criterion.

Seroresponse Rate to Omicron BA.1 Strain

In the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination, majority in each arm, achieved seroresponse to Omicron variant at 1 month after the study vaccination.

The lower bound of the 2-sided 95% CI for the difference in seroresponse rates was greater than the prespecified margin of -5% for noninferiority for all Omicron-modified vaccine groups evaluated (monovalent and bivalent). The lower bound of the 2-sided 95% CI was greater than 0%, suggesting higher seroresponse to Omicron variant compared to BNT162b2 30 µg recipients.

Difference in seroresponse rate from the sensitivity analysis stratified by baseline assay result category are similar to the unadjusted results. Difference in seroresponse rate reported in the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination was similar.

Noninferiority based on seroresponse for BNT162b2 OMI 60 µg, bivalent BNT162b2 + BNT162b2 OMI 60 µg, and bivalent BNT162b2 + BNT162b2 OMI 30 µg to BNT162b2 30 µg were met, as the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5% for each of the three comparisons.

Although not formally claimed due to multiplicity, monovalent Omicron-modified vaccine BNT162b2 OMI 30 µg also had lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse (>-5%) consistent with noninferiority criterion.

Table 6. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

					Difference	
Assay	**Vaccine Group (as Randomized)**	**Sampling Time Point[a]**	**N[b]**	**n[c] (%) (95% CI[d])**	**%[e]**	**(95% CI[f])**
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	BNT162b2 (30 µg)	1 Month	149	85 (57.0) (48.7, 65.1)		
	BNT162b2 OMI (30 µg)	1 Month	163	125 (76.7) (69.4, 82.9)	19.6	(9.3, 29.7)
	BNT162b2 OMI (60 µg)	1 Month	166	143 (86.1) (79.9, 91.0)	29.1	(19.4, 38.5)
	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)	1 Month	169	121 (71.6) (64.2, 78.3)	14.6	(4.0, 24.9)
	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)	1 Month	162	110 (67.9) (60.1, 75.0)	10.9	(0.1, 21.4)

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: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Seroresponse is defined as achieving ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered a seroresponse.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
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 prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
c. n = Number of participants with seroresponse at 1 month after vaccination for the given assay.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (vaccine group in the corresponding row - BNT162b2 [30 µg]).
f. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
PFIZER CONFIDENTIAL SDTM Creation: 12JUL2022 (18:57) Source Data: adva Table Generation: 12JUL2022 (23:08)
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Noninferiority of Anti-Reference Strain Immune Responses

The noninferiority immunogenicity objectives on anti–reference strain immune responses were to assess the noninferiority of the anti–reference strain immune response induced by a dose of bivalent Original/Omicron BA1 (15/15 µg or 30/30 µg) relative to the anti–reference strain immune response elicited by a dose of Original at 30 µg given as a fourth dose in Original Comirnaty 30 µg -experienced participants >55 years of age.

GMR of Reference Strain Neutralizing Titers

In the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination, GMRs for the two bivalent vaccine groups 15/15 µg and 30/30 µg to Original 30 µg group was 0.99 (2-sided 95% CI: 0.82, 1.20) and 1.30 (2-sided 95% CI: 1.07, 1.58), respectively.

Noninferiority based on the GMR for reference strain response was met by both bivalent vaccine groups as the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion).

GMRs from the sensitivity analysis using linear regression model with terms of baseline assay results (log scale) and vaccine group are similar to the unadjusted GMR. GMR reported in the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination and participants in the all-available population were similar.

SARS-CoV-2 Omicron- or Reference-Strain–Neutralizing Titers

GMTs

Omicron Neutralizing Titers

In the evaluable immunogenicity population without evidence of infection up to 1 month post-dose, GMTs were substantially elevated over levels observed before study vaccination for Omicron BA.1, across all groups, with monovalent Omicron BA1 30 µg and 60 µg groups and bivalent 30/30 µg group showing the best responses against Omicron BA.1 (Table 7).

Reference Strain Neutralizing Titers

In the evaluable immunogenicity population without evidence of infection up to 1 month post-dose, GMTS were substantially elevated over levels observed before study vaccination for the reference strain, across all vaccine groups.

Figure 1. Geometric Mean Titers and 95% CIs: SARS-CoV-2 Neutralization Assay – Omicron BA.1 – NT50 – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

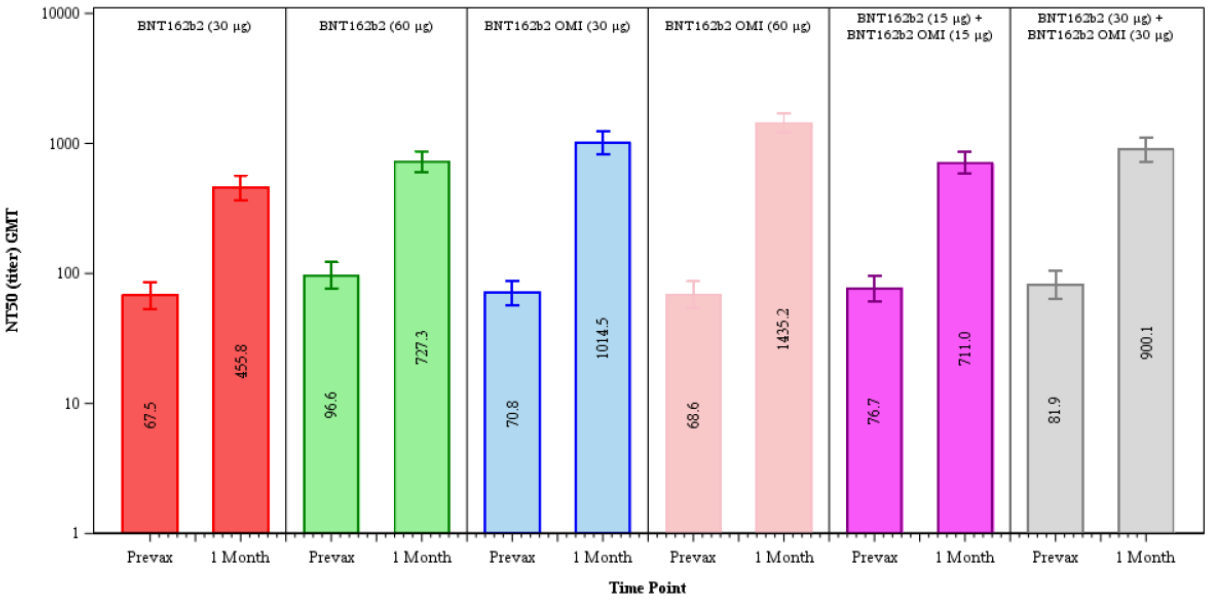

Figure 2. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay – Reference Strain – NT50 – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

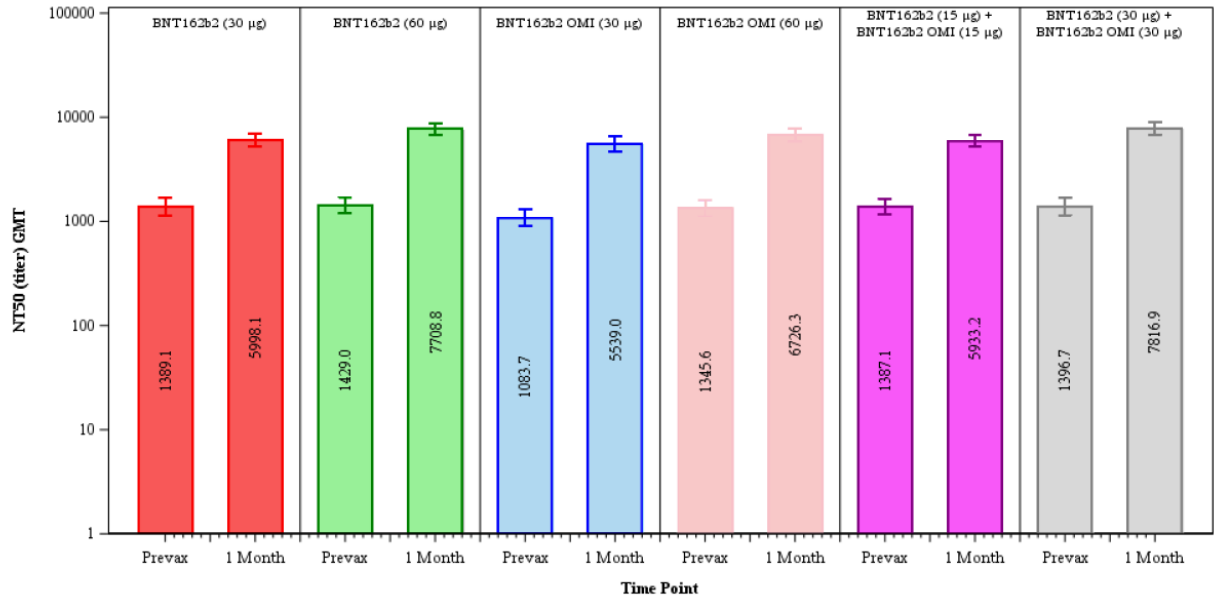

Table 7. Geometric Mean Titers – Participants without evidence of infection up to 1 month after the study vaccination – Expanded Cohort – Immunogenicity Subset – Participants>55 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)											
		BNT162b2 (30 µg)		BNT162b2 (60 µg)		BNT162b2 OMI (30 µg)		BNT162b2 OMI (60 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)	
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])	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.1 - NT50 (titer)	Prevax	167	67.5 (52.9, 86.3)	188	96.6 (76.7, 121.7)	174	70.8 (57.4, 87.4)	176	68.6 (54.3, 86.8)	177	76.7 (61.1, 96.1)	168	81.9 (63.9, 104.9)
	1 Month	163	455.8 (365.9, 567.6)	185	727.3 (606.0, 872.9)	169	1014.5 (825.6, 1246.7)	174	1435.2 (1208.1, 1704.8)	178	711.0 (588.3, 859.2)	175	900.1 (726.3, 1115.6)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	Prevax	179	1389.1 (1142.1, 1689.5)	197	1429.0 (1193.4, 1711.0)	176	1083.7 (896.1, 1310.7)	182	1345.6 (1120.1, 1616.5)	186	1387.1 (1158.9, 1660.2)	179	1396.7 (1149.9, 1696.3)
	1 Month	182	5998.1 (5223.6, 6887.4)	198	7708.8 (6772.3, 8774.7)	180	5539.0 (4715.0, 6506.9)	184	6726.3 (5832.9, 7756.6)	186	5933.2 (5188.2, 6785.2)	180	7816.9 (6820.7, 8958.6)

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: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
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.
PFIZER CONFIDENTIAL SDTM Creation: 12JUL2022 (18:57) Source Data: adva Table Generation: 12JUL2022 (23:07)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2 ube/C4591031 E 1MINEXP EUA/adva s001 exp awo 1m

GMFRs

Omicron Neutralizing Titers

In participants without evidence of SARS-CoV-2 infection up to 1 month post-Dose, the GMFRs for the Omicron variant were higher for the monovalent Omicron BA1 30 µg and 60 µg groups and the bivalent Original/Omicron BA1. 15/15 µg and 30/30 µg groups compared with the Original 30 µg and 60 µg groups. GMFRs were:

- Original 30 µg and 60 µg groups: 5.8 and 6.9, respectively
- Omicron BA130 µg and 60 µg groups: 13.5 and 19.6, respectively
- Original/Omicron BA1. 15/15 µg and 30/30 µg groups: 9.1 and 10.9, respectively.

Reference Strain Neutralizing Titers

In participants without evidence of SARS-CoV-2 infection up to 1-month post-Dose, the GMFRs for the reference strain were similar across all vaccine groups.

Table 8. Geometric Mean Fold Rises From Before the Study Vaccination to Each Subsequent Time Point – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)											
		BNT162b2 (30 µg)		BNT162b2 (60 µg)		BNT162b2 OMI (30 µg)		BNT162b2 OMI (60 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)	
Assay	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])	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.1 - NT50 (titer)	1 Month	149	5.8 (4.6, 7.2)	175	6.9 (5.8, 8.3)	163	13.5 (10.6, 17.3)	166	19.6 (15.4, 25.1)	169	9.1 (7.3, 11.2)	162	10.9 (8.5, 13.9)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	1 Month	179	4.3 (3.7, 5.0)	197	5.4 (4.6, 6.3)	176	5.2 (4.4, 6.2)	181	5.0 (4.2, 6.0)	186	4.3 (3.6, 5.1)	178	5.6 (4.7, 6.6)

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: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
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.
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(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2 ube/C4591031 E 1MINEXP EUA/adva s002 exp awo 1m

Seroresponse to Omicron - or Reference-Strain

In the expanded cohort of participants without evidence of SARS-CoV-2 infection up to 1 month after study vaccination, the proportion of participants who achieved seroresponse in SARS-CoV-2 50% neutralizing titers at 1 month post-Dose for the Omicron variant was highest for the monovalent Omicron BA1. 30 µg, 60 µg and bivalent Original/Omicron BA1.15/15 µg groups (76.7%, 86.1% and 71.6%, respectively).

The proportion of participants who achieved seroresponse in SARS-CoV-2 50% neutralizing titers at 1 month post-Dose for the reference strain were generally higher in the 60 µg groups than in the respective 30 µg groups.

Table 9. Number (%) of Participants Achieving Seroresponse – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)											
		BNT162b2 (30 µg)		BNT162b2 (60 µg)		BNT162b2 OMI (30 µg)		BNT162b2 OMI (60 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)	
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])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	1 Month	149	85 (57.0) (48.7, 65.1)	175	108 (61.7) (54.1, 68.9)	163	125 (76.7) (69.4, 82.9)	166	143 (86.1) (79.9, 91.0)	169	121 (71.6) (64.2, 78.3)	162	110 (67.9) (60.1, 75.0)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	1 Month	179	88 (49.2) (41.6, 56.7)	197	115 (58.4) (51.2, 65.3)	176	98 (55.7) (48.0, 63.2)	181	104 (57.5) (49.9, 64.8)	186	93 (50.0) (42.6, 57.4)	178	110 (61.8) (54.2, 69.0)

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: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Seroresponse is defined as achieving ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered a seroresponse.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
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 prevaccination 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.
PFIZER CONFIDENTIAL SDTM Creation: 12JUL2022 (18:57) Source Data: adva Table Generation: 12JUL2022 (23:25)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2 ube/C4591031 E 1MINEXP EUA/adva s003 exp awo 1m

Subgroup Analyses

Overall, for all BNT162b2, BNT162b2 OMI and BNT162b2 OMI + BNT162b2 recipients, there were no clinically meaningful differences between subgroups for neutralizing GMTs and seroresponse rates, for the Omicron variant and reference strain except for baseline SARS-CoV-2 status. As several subgroups (eg, younger age group, Black or African American, Asian, Hispanic/Latino, SARS-CoV-2 baseline positive or NAAT positive participants) included a limited number of participants, their results should be interpreted with caution.

- GMTs at 1 month-post-Dose were substantially higher for participants who were baseline positive compared to those who were baseline negative for SARS-CoV-2.
- GMFRs at 1 month-post-Dose were generally lower for participants who were baseline positive as the baseline titers compared to those who were baseline negative for SARS-CoV-2.
- Seroresponse rates at 1 month-post-Dose were generally lower for participants who were baseline positive compared to those who were baseline negative for SARS-CoV-2.

Surveillance of COVID-19 Cases – Expanded Cohort

<u>COVID-19 Cases up to Data Cutoff Date</u>

In the expanded cohort, cases in a total of 30 participants across all vaccine groups were accrued up to the data cutoff date of 16 May 2022.

Original 30 µg and 60 µg groups: 7 and 6 cases, respectively

Omicron BA1. 30 µg and 60 µg groups: 7 and 3 cases, respectively

Original/BA1. 15/15 µg and 30/30 µg groups: 1 and 6 cases, respectively.

The majority of cases (n=29) met both protocol-defined and CDC defined criteria for COVID-19 disease. One case in the BNT162b2 + BNT162b2 OMI 60 µg group met only the CDC-defined criteria (Appendix 16.2.8.1). The reported signs and symptoms were generally similar for participants in the BNT162b2, BNT162b2 OMI and BNT162b2 + BNT162b2 OMI groups, and the most commonly reported were new or increased cough (n=19) and sore throat (n=19). Few participants reported >3 concurrent signs and symptoms (n=8). No cases meeting severe criteria per the FDA or CDC definition were observed in any of the vaccine groups.

Immunogenicity results for the expanded BA4/ BA5 cohort

GMT

Overall, the observed Omicron BA.4/BA.5 neutralizing GMTs at 1 month post-Dose were numerically slightly higher for the bivalent Original/Omicron BA1. 15/15 µg group compared to Original 30 µg group (167.4 vs 155.1).

GMTs at pre-Dose and 1 month-post-Dose were generally higher for participants who were baseline seropositive compared to those who were baseline seronegative for SARS-CoV-2 (Table 10).

Table 10. Geometric Mean Titers, by Baseline SARS-CoV-2 Status – Expanded Cohort – Descriptive Omicron BA.4/BA.5 Neutralization Assay Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			BNT162b2 (30 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)	
Assay	Baseline 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 BA.4/BA.5 - NT50 (titer)	All	Prevax	100	46.8 (34.5, 63.4)	100	37.3 (28.0, 49.7)
		1 Month	100	**155.1** (122.2, 196.8)	100	**167.4** (128.0, 218.9)
	Positive[d]	Prevax	20	355.1 (179.8, 701.0)	20	211.1 (92.5, 481.6)
		1 Month	20	607.6 (380.3, 970.7)	20	774.4 (410.5, 1460.9)
	Negative[e]	Prevax	80	28.2 (22.2, 35.7)	80	24.2 (19.5, 30.0)
		1 Month	80	110.2 (88.5, 137.3)	80	114.1 (90.3, 144.3)

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.
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.
Participants selected for this subgroup also had no evidence of SARS-CoV-2 infection up to 1 month after the study vaccination (N-binding antibody [serum] result negative at baseline and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at baseline and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection, and no medical history of COVID-19).
PFIZER CONFIDENTIAL SDTM Creation: 05AUG2022 (16:25) Source Data: adva Table Generation: 08AUG2022 (12:08) (Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2_ube/C4591031_E_1MINEXP_BA4_5/adva_s001_exp_evl_1m_nv

GMFRs

Overall, GMFRs at 1 month post-Dose for Omicron BA.4/BA.5 were numerically slightly higher for the bivalent Original/Omicron BA1. 15/15 µg group compared to the Original 30 µg group (4.5 vs 3.3).

GMFRs at 1 month-post-Dose were generally lower for participants who were baseline seropositive compared to those who were baseline seronegative.

Table 11. Geometric Mean Fold Rises From Before the Study Vaccination to 1 Month After the Study Vaccination, by Baseline SARS-CoV-2 Status – Expanded Cohort – Descriptive Omicron BA.4/BA.5 Neutralization Assay Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			BNT162b2 (30 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)	
Assay	Baseline 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 BA.4/BA.5 - NT50 (titer)	All	1 Month	100	3.3 (2.8, 4.0)	100	4.5 (3.7, 5.5)
	Positive[d]	1 Month	20	1.7 (1.2, 2.5)	20	3.7 (2.1, 6.3)
	Negative[e]	1 Month	80	3.9 (3.3, 4.7)	80	4.7 (3.8, 5.9)

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.
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 prevaccination 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. Participants selected for this subgroup also had no evidence of SARS-CoV-2 infection up to 1 month after the study vaccination (N-binding antibody [serum] result negative at baseline and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at baseline and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection, and no medical history of COVID-19).
PFIZER CONFIDENTIAL SDTM Creation: 05AUG2022 (16:25) Source Data: adva Table Generation: 08AUG2022 (12:10) (Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2_ube/C4591031_E_1MINEXP_BA4_5/adva_s002_exp_evl_1m_nv

Seroresponse

The proportion of participants who achieved seroresponse in Omicron BA.4/BA.5 50% neutralizing titers at 1 month post-Dose was higher for the bivalent Original/Omicron BA1. 15/15 µg group compared to Original 30 µg group (56% vs 42%).

Seroresponse rates at 1 month-post-Dose were generally lower for participants who were baseline seropositive compared to those who were baseline seronegative.

Table 12. Number (%) of Participants Achieving Seroresponse, by Baseline SARS-CoV-2 Status – Expanded Cohort – Descriptive Omicron BA.4/BA.5 Neutralization Assay Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			BNT162b2 (30 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)	
Assay	Baseline 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 BA.4/BA.5 - NT50 (titer)	All	1 Month	100	42 (42.0) (32.2, 52.3)	100	56 (56.0) (45.7, 65.9)
	Positive[e]	1 Month	20	5 (25.0) (8.7, 49.1)	20	10 (50.0) (27.2, 72.8)
	Negative[f]	1 Month	80	37 (46.3) (35.0, 57.8)	80	46 (57.5) (45.9, 68.5)

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: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the prevaccination 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. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
f. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19. Participants selected for this subgroup also had no evidence of SARS-CoV-2 infection up to 1 month after the study vaccination (N-binding antibody [serum] result negative at baseline and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at baseline and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection, and no medical history of COVID-19).
PFIZER CONFIDENTIAL SDTM Creation: 05AUG2022 (16:25) Source Data: adva Table Generation: 08AUG2022 (12:11) (Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2_ube/C4591031_E_1MINEXP_BA4_5/adva_s003_exp_evl_1m_nv

Immunogenicity Results: Sentinel Cohort

GMTs for Omicron, Reference Strain, and Delta Variants (Sentinel Cohort)

Among participants >55 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the observed GMT at 1-month post-dose against Omicron variants (BA.1, BA.2, BA.2.12.1, and BA.4/BA.5) were the lowest for the monovalent BNT16b2 OMI 30 µg and the BNT162b2 30 µg groups (Table 13). All bivalent vaccine groups showed in general higher neutralization titers to Omicron variants. Omicron BA.4/BA.5 was the least effectively neutralized variant for all vaccine groups, though titers were slightly higher in the Omicron-modified vaccine groups compared to the prototype vaccine. Similar results were observed for participants with and without evidence of prior SARS-CoV-2 infection in the evaluable immunogenicity population and participants in the all-available immunogenicity population.

Table 13. Geometric Mean Titers – Additional Omicron Variants – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Sentinel Cohort – Participants >55 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)									
		BNT162b2 (30 µg)		BNT162b2 OMI (30 µg)		BNT162b2 OMI (60 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)	
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])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.1 - NT50 (titer)	1 Month	17	425.7 (226.6, 799.9)	17	501.1 (231.8, 1083.4)	18	822.0 (403.6, 1674.3)	13	771.3 (387.9, 1533.6)	18	678.1 (394.1, 1166.6)
SARS-CoV-2 FFRNT - Omicron BA.2 - NT50 (titer)	1 Month	17	384.4 (223.5, 661.3)	17	245.5 (123.6, 487.4)	18	470.3 (232.6, 951.0)	13	560.1 (305.0, 1028.6)	18	419.0 (255.9, 686.0)
SARS-CoV-2 FFRNT - Omicron BA.2.12.1 - NT50 (titer)	1 Month	17	354.3 (200.5, 626.4)	17	294.9 (134.8, 645.4)	18	443.9 (227.1, 867.6)	13	575.3 (292.8, 1130.2)	18	461.3 (279.9, 760.4)
SARS-CoV-2 FFRNT - Omicron BA.4/BA.5 - NT50 (titer)	1 Month	17	110.9 (67.9, 180.9)	17	78.4 (42.8, 143.7)	18	145.3 (74.7, 282.8)	13	226.3 (120.7, 424.1)	18	137.2 (77.3, 243.5)

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: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the study vaccination, 7-days post-study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
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.
PFIZER CONFIDENTIAL SDTM Creation: 04JUN2022 (08:36) Source Data: adva Table Generation: 12JUN2022 (22:08)
(Data cutoff date : 05APR2022 Database snapshot date : 02MAY2022) Output File: ./nda3/C4591031_E_1MSentinel_NV/adva_s001_sen_awo_1mn

For sentinel cohort participants in the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination, GMTs at 1-month post-dose were substantially elevated over levels observed before study vaccination for Omicron BA.1, reference strain and Delta across all groups, with Omicron BA1. 60 µg group and Original/ Omicron BA1. 15/15 µg and 30/30 µg groups showing the best responses against Omicron BA.1 (Table 14).

Table 14. Geometric Mean Titres – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Sentinel Cohort – Participants >55 Year of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)											
		BNT162b2 (30 µg)		BNT162b2 (60 µg)		BNT162b2 OMI (30 µg)		BNT162b2 OMI (60 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)	
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])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.1 - NT50 (titer)	Prevax	17	52.1 (31.1, 87.5)	20	63.9 (29.0, 140.7)	17	47.1 (23.1, 96.1)	18	52.4 (27.0, 101.6)	12	100.8 (68.2, 149.0)	18	52.4 (30.7, 89.3)
	1 Month	17	614.4 (311.8, 1210.6)	20	485.0 (301.5, 780.2)	17	602.0 (295.0, 1228.7)	18	996.6 (495.4, 2004.8)	12	1356.1 (655.9, 2803.6)	18	922.7 (571.9, 1488.6)
SARS-CoV-2 FFRNT - reference strain - NT50 (titer)	Prevax	17	208.6 (106.9, 406.9)	20	255.5 (127.0, 513.8)	17	221.7 (119.8, 410.3)	18	226.3 (114.7, 446.3)	12	369.7 (232.4, 588.2)	18	172.8 (105.2, 283.9)
	1 Month	17	1810.2 (946.3, 3462.7)	20	1718.5 (1174.6, 2514.1)	17	962.2 (520.3, 1779.4)	18	1522.2 (809.2, 2863.4)	12	2560.0 (1492.8, 4390.3)	18	1522.2 (1071.6, 2162.2)
SARS-CoV-2 FFRNT - Delta - NT50 (titer)	Prevax	17	150.5 (78.1, 289.9)	20	234.3 (113.0, 485.6)	17	208.6 (103.5, 420.1)	18	217.7 (118.8, 398.9)	12	329.4 (205.1, 529.0)	18	154.0 (90.5, 262.0)
	1 Month	17	1668.4 (870.8, 3196.7)	20	1631.4 (1043.5, 2550.6)	17	982.0 (490.3, 1966.7)	18	1741.8 (929.5, 3264.2)	12	2873.5 (1527.1, 5407.2)	18	1436.8 (912.4, 2262.5)

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: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the study vaccination, 7-days post-study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

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.

PFIZER CONFIDENTIAL SDTM Creation: 05MAY2022 (16:36) Source Data: adva Table Generation: 09MAY2022 (00:37)
(Data cutoff date : 05APR2022 Database snapshot date : 02MAY2022) Output File: ./nda3/C4591031_E_1MSentinel/adva_s001_sen_awo_1m

GMFRs for Omicron BA.1, Reference Strain, and Delta Variants (Sentinel Cohort)

For sentinel cohort participants in the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination, the GMFRs from before study vaccination to 1 month post-Dose ranged from 7.6 to 19.0 for the Omicron BA.1 variant, 4.3 to 8.8 for reference strain and 4.7 to 11.1 for the Delta variant. GMFRs were less consistent across vaccine groups, potentially a reflection of the small sample size in the sentinel groups.

Seroresponse to Omicron BA.1, Reference Strain, and Delta Variants (Sentinel Cohort)

For sentinel cohort participants in evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination, the proportion of participants achieving seroresponse to Omicron BA.1, reference strain, and Delta at 1 month post-Dose were generally similar across all vaccine groups, with the Omicron BA1. 30 µg slightly lower for the reference strain and Delta variant, and the Original/ Omicron BA1. 15/15 µg group slightly lower for the Delta variant.

Table 15. Number (%) of Participants Achieving Seroresponse – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Sentinel Cohort – Participants >55 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)											
		BNT162b2 (30 µg)		BNT162b2 (60 µg)		BNT162b2 OMI (30 µg)		BNT162b2 OMI (60 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)	
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])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 FFRNT - Omicron BA.1 - NT50 (titer)	1 Month	17	15 (88.2) (63.6, 98.5)	20	14 (70.0) (45.7, 88.1)	17	15 (88.2) (63.6, 98.5)	18	15 (83.3) (58.6, 96.4)	12	11 (91.7) (61.5, 99.8)	18	18 (100.0) (81.5, 100.0)
SARS-CoV-2 FFRNT - reference strain - NT50(titer)	1 Month	17	15 (88.2) (63.6, 98.5)	20	15 (75.0) (50.9, 91.3)	17	10 (58.8) (32.9, 81.6)	18	13 (72.2) (46.5, 90.3)	12	9 (75.0) (42.8, 94.5)	18	17 (94.4) (72.7, 99.9)
SARS-CoV-2 FFRNT - Delta - NT50 (titer)	1 Month	17	15 (88.2) (63.6, 98.5)	20	15 (75.0) (50.9, 91.3)	17	10 (58.8) (32.9, 81.6)	18	14 (77.8) (52.4, 93.6)	12	8 (66.7) (34.9, 90.1)	18	18 (100.0) (81.5, 100.0)

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: Seroresponse is defined as achieving ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered a seroresponse.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the study vaccination, 7-days post-study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
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 prevaccination 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.
PFIZER CONFIDENTIAL SDTM Creation: 05MAY2022 (16:36) Source Data: adva Table Generation: 07MAY2022 (05:50)
(Data cutoff date : 05APR2022 Database snapshot date : 02MAY2022) Output File: ./nda3/C4591031_E_1MSentinel/adva_s003_sen_awo_1m

Additional descriptive analyses from Substudy E were performed to further characterize BA.2.75 neutralization responses following a booster (fourth) dose of bivalent Original/Omicron BA.1-15/15 µg compared to the prototype vaccine (BNT162b2 30 µg). A fluorescent focus reduction neutralization test (FFRNT) was used to determine Omicron BA.2.75-specific neutralizing titers in a small subset of C4591031 Substudy E (Expanded Cohort: participants >55 years of age).

The evaluable immunogenicity population for the Omicron BA.2.75 neutralization assay subset included a total of 30 participants each arm who were randomly selected from the expanded cohort evaluable immunogenicity population without evidence of infection up to 1 month after study vaccination. Demographic characteristics for participants in this subset were similar between the two vaccine groups.

BNT162b2 OMI 30 µg group who were randomly selected from the expanded cohort evaluable immunogenicity population without evidence of infection up to 1 month after study vaccination. Demographic characteristics for participants in this subset were similar between the two vaccine groups BNT162b2 OMI 30 µg group who were randomly selected from the expanded cohort evaluable immunogenicity population without evidence of infection up to 1 month after study vaccination. Demographic characteristics for participants in this subset were similar between the two vaccine groups. Overall, the observed Omicron BA.2.75 neutralizing GMTs at 1-month post-Dose in participants without evidence of infection were numerically higher for the bivalent Original/Omicron BA.1 15/15 µg group compared to Original group (108.0 vs 88.8) (Table 16 below).

Table 16. Geometric Mean Titres – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Descriptive Omicron BA.2.75 Neutralization Assay Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)			
		BNT162b2 (30 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)	
Assay	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.2.75 - NT50 (titer)	1 Month	30	88.8 (57.7, 136.5)	30	108.0 (71.0, 164.4)

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: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, a negative N-binding antibody [serum] result at the study vaccination and the 1-month post–study vaccination visits, a negative NAAT [nasal swab] result at the study vaccination visit and at any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
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.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2022 (15:54) Source Data: adva Table Generation: 17AUG2022 (02:31)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File:
./nda2 ube/C4591031 E 1MINEXP BA 2 75/adva s001 exp evl 1m nv2

Immunogenicity conclusions for Expanded Cohort

Overall, for the primary and secondary immunogenicity analyses for the Omicron variant, BNT162b2 OMI 30 µg and 60 µg and the BNT162b2 +BNT162b2 OMI 30 µg and 60 µg groups met the prespecified criteria for superiority with respect to GMR and noninferiority with respect to seroresponse rate when compared to BNT162b2 30 µg group, when administered to BNT162b2-experienced participants as fourth dose.

- 'Simple' superiority of BNT162b2 OMI 60 µg, bivalent BNT162b2 + BNT162b2 OMI 60 µg, and bivalent BNT162b2 + BNT162b2 OMI 30 µg to BNT162b2 30 µg were met, as the lower bound of the 2-sided 95% CI for GMR was >1 for each of the three comparisons.
- Noninferiority based on seroresponse for BNT162b2 OMI 60 µg, bivalent BNT162b2 + BNT162b2 OMI 60 µg, and bivalent BNT162b2 + BNT162b2 OMI 30 µg to BNT162b2 30 µg were met, as the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5% for each of the three comparisons. Although not formally claimed due to multiplicity, monovalent Omicron-modified vaccine BNT162b2 OMI 30 µg also had lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse (>-5%) consistent with noninferiority criterion.
- "Super" superiority of BNT162b2 OMI 60 µg to BNT162b2 30 µg for the Omicron variant was achieved based on the prespecified criterion, as the lower bound of the 2- sided 95% CI for GMR was >1.5. Although not formally claimed due to multiplicity, monovalent Omicron-modified vaccine BNT162b2 OMI 30 µg also had GMR and lower bound of 95% CI (>1.5) consistent with the super superiority criterion.
- Noninferiority for reference strain based on the GMR was met in both bivalent vaccine groups (BNT162b2 + BNT162b2 OMI 30 µg and 60 µg) as the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion).
- Overall, for all BNT162b2, BNT162b2 OMI and BNT162b2 OMI + BNT162b2 recipients, there were no clinically meaningful differences between subgroups for neutralizing GMTs and seroresponse rates, for the Omicron variant except for baseline SARS-CoV-2 status. GMTs at 1

month-post-Dose were substantially higher while seroresponse rates were generally lower for participants who were baseline positive compared to those who were baseline negative for SARS-CoV-2.

- GMTs at 1 month post-Dose were substantially elevated over levels observed before study vaccination for Omicron BA.1, across all groups, with monovalent BNT162b2 OMI 30- and 60 µg and bivalent BNT162b2 + BNT162b2 OMI 30- and 60 µg showing the best responses against Omicron BA.1. GMFRs were higher for the monovalent BNT162b2 OMI and the bivalent Omicron-modified vaccine groups compared with the BNT162b2 groups.
- GMTs at 1 month post-Dose were substantially elevated over levels observed before study vaccination for the reference strain, across all groups; BNT162b2, BNT162b2 OMI and BNT162b2 + BNT162b2 OMI 60 µg elicited higher responses against the reference strain. GMFRs for the reference strain were similar across all vaccine groups.
- Overall, for participants >55 years of age in the expanded group, few COVID-19 cases accrued up to the data cutoff date of 16 May 2022. The study was not powered to assess differences across vaccine groups on COVID-19 cases.

Sentinel Cohort

- Among participants >55 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, Omicron BA.4/BA.5 was the least effectively neutralized variant for all vaccine groups, though titers were slightly higher in the Omicron-modified vaccine groups compared to the prototype vaccine.
- All bivalent vaccine groups showed in general higher neutralization titers to Omicron variants. GMTs at 1-month post-Dose were substantially elevated over levels observed before study vaccination for Omicron BA.1, reference strain and Delta across all groups, with monovalent 60 µg Omicron and bivalent Omicron-modified vaccines showing the best responses against Omicron BA.1. GMTs for reference strain and Delta were well preserved across all Omicron-modified vaccine groups.
- Seroresponse was generally similar across all groups, with the BNT162b2 OMI 30 µg slightly lower for the reference strain and Delta variant, and the BNT162b2 + BNT162b2 OMI 30 group slightly lower for the Delta variant. GMFRs were less consistent across vaccine groups, potentially a reflection of the small sample size in the sentinel groups.

4.2 Study C4591031 Substudy D

4.2.1 Methods

Conduct of the study

C4591031 Protocol Amendment 8 was the effective protocol version at the time of the data cutoff and data analyses included in this Substudy D interim report for Cohort 2.

Study participants

Participants in Cohort 2 were enrolled from Study C4591001 and C4591031 Substudy A and completed a 2-dose primary series and received a single booster (third) dose of BNT162b2, with their last dose 90 to 180 days prior to randomization. Approximately 600 participants were to be

randomized at a ratio of 1:1 to receive a fourth dose (ie, first study vaccination booster) of either BNT162b2 or BNT162b2 OMI at Visit 401. Participants were offered a dose of BNT162b2 OMI at Visit 404 (3-month follow-up). Randomization was stratified by age (18-30, 31-55 years of age). Cohort 2 was observer-blinded.

Participants in C4591031 Substudy D were enrolled at sites in the US and South Africa, the latter where the new SARS-CoV-2 variant, B.1.1.529, was first identified. The sample size for Groups 3 and 4 (Cohort 2) was based on consideration of an acceptable safety database and power for the primary and secondary immunogenicity objectives

Table 17. Total Number of Participants by Cohort

Cohort	Group	Prior BNT162b2 Experience	Vaccine	Number of Doses Administered as Part of Substudy D	Total Number of Participants
Cohort 1	Group 1	2 Doses	BNT162b2 OMI	1	205
	Group 2	2 Doses	BNT162b2 OMI	2	205
	Group 2b	2 Doses	BNT162b2	1	205
Cohort 2	Group 3	3 Doses	BNT162b2 OMI	1 or 2	300
	Group 4	3 Doses	BNT162b2 (and BNT162b2 OMI at Visit 404)	1 or 2	300
Cohort 3	Group 5	Naïve	BNT162b2 OMI	3	205

Note: Cohorts 1 and 2 were observer-blinded. Participants in Cohort 1 were to remain blinded to whether they were going to receive a fourth dose through 1 month after their first dose. Cohort 2 participants were to be unblinded once they completed Visit 404. Cohort 3 was open-labelled.

Participants must have met all of the general inclusion and exclusion criteria as specified for the master protocol and the Substudy D-specific criteria. The enrolled in Cohort 2 of this substudy were healthy participants ≥18 to ≤55 years of age enrolled from Study C4591001 and C4591031 Substudy A who received 3 prior doses of 30 µg BNT162b2, with the third dose being 90 to 180 days before Visit 401 (Day 1) in C4591031 Substudy D.

Table 18. Substudy D Immunogenicity Objectives, Estimands and Endpoints

Objectives	Estimands	Endpoints
Primary Immunogenicity ***BNT162b2-experienced participants***		
G3vG4A: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response after 1 dose of BNT162b2 OMI compared to after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of 1 dose of study intervention) of past SARS-CoV- 2 infection: • GMR of the Omicron-neutralizing titers at 1 month after 1 dose of BNT162b2 OMI to those at 1 month after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse[b] to the Omicron variant at 1 month after 1 dose of BNT162b2 OMI and at 1 month after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants	SARS-CoV-2 Omicron-neutralizing titers

G3vG4B: To demonstrate the "super" superiority of the anti-Omicron immune response after 1 dose of BNT162b2 OMI compared to after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants	Same as GMR estimand of G3vG4A	Same as G3vG4A
Exploratory		
To describe the immune response to BNT162b2 OMI or BNT162b2 given as the third and/or fourth and/or fifth dose in BNT162b2-experienced participants[a]	• GMT at each time point • GMFRs from before the first dose of study intervention to subsequent time points • Percentages of participants with seroresponse[b] at each time point	• SARS-CoV-2 Omicron-neutralizing titers • SARS-CoV-2 reference-strain–neutralizing titers
To describe the immune response to the reference strain and VOCs in a subset of 30 participants[c] per group[a]		• SARS-CoV-2 neutralizing titers for the reference strain and VOCs
To describe confirmed COVID-19 and severe COVID-19 cases[a,d]		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases

[a] Results included in this interim CSR are for BNT162b2-experienced participants given a fourth dose of BNT162b2 OMI or BNT162b2 (Group 3 and Group 4, respectively).

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

[c] This subset of participants will not contribute to the assessment of primary and secondary immunogenicity objectives.

[d] Results included in this interim CSR are up to the data cutoff date, which represents up to at least 1 month of follow-up after fourth dose.

AE results up to the data cutoff date are also included.

Sample size

The sample size for Groups 3 and 4 of Cohort 2 was based on consideration of an acceptable safety database and power for the primary and secondary immunogenicity objectives. For each group, a subset of 30 participants out of 300 participants total was to be selected as a sentinel group for separate assessment of immune response defined in an exploratory objective. The subset was to comprise the first 30 participants from each group with immunogenicity samples received by the central laboratory. A random sample of 175 participants from each of Groups 3 and 4 selected from the remaining approximately 270 participants was used for evaluation of the primary and secondary immunogenicity objectives in each group.

For comparisons based on GMR, common assay standard deviations at 1 month after the third or fourth dose or 1 month after Dose 2 in log scale is assumed to be 0.93 based on data observed in the C4591001 study. If the true GMR of Omicron-neutralizing titer after BNT162b2 OMI to after BNT162b2 is 1.5, 114 evaluable participants per group would provide 90.6% power to declare

superiority. If the true GMR is 2.5, the study would have 98.5% power to declare "super" superiority using a 1.5-fold margin. For comparisons based on seroresponse rate difference, if the seroresponse rate is 80% in the BNT162b2 OMI group and 60% in the BNT162b2 group, the study had 98.6% power to demonstrate noninferiority using a 5% margin.

Randomisation
For Cohort 2, participants received 1 dose of study intervention as allocated by the IRT at Visit 401. Group 3 and Group 4 participants could receive a dose of BNT162b2 OMI at Visit 404.

Blinding
In Cohort 2, the study staff receiving, storing, dispensing, preparing, and administering the study interventions were unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, were blinded to study intervention assignments. In particular, the individuals who evaluated participant safety were blinded.

The majority of sponsor/Pfizer staff were blinded to study intervention allocation for Cohort 2. All laboratory testing personnel performing serology assays remained blinded to study intervention assigned/received throughout the study.

Per protocol, participants in Cohort 2 were to be unblinded to confirm the vaccine received once they complete Visit 404 (3 months after Substudy D Vaccination 1).

Immunogenicity evaluation

Immunogenicity evaluation for substudy D was identical as described for substudy E. Shortly, Immunogenicity results for non-sentinel analyses were based on validated assays for 50% SARS-CoV-2 neutralizing titers on a newly developed 384-well assay platform (reference strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.1) at before first study (Dose 4) vaccination and 1 month after first study (Dose 4) vaccination with BNT162b2 OMI or BNT162b2, reported as GMTs, GMRs, percentages/difference in percentages with seroresponse, GMFRs.

A non-validated assay (FFRNT) was used to obtain sentinel SARS-CoV-2 serum neutralization titers from a subset of 60 participants in Groups 3 and 4 of Cohort 2, before Dose 4 and at 1 month post-Dose 4.

Immunogenicity Endpoints and analysis methods

Immunogenicity analyses were conducted based on the evaluable and all-available immunogenicity populations. Immunogenicity results were based on validated assays for 50% SARS-CoV-2 neutralizing titers from before Dose 4 to 1 month after Dose 4 of BNT162b2 OMI or BNT162b2, reported as:

- Geometric mean titers (GMTs)
- Geometric mean ratio (GMR) of GMTs (BNT162b2 OMI / BNT162b2)
- Percentages/difference in percentages with seroresponse (BNT162b2 OMI – BNT162b2)
- Geometric mean-fold rises (GMFRs) in titers

A supportive FFRNT assay was used to obtain sentinel Omicron neutralization titers from a subset of participants in Study C4591031 Substudy D.

The primary immunogenicity objective for Cohort 2 (BNT162b2 OMI vs BNT162b2) was to demonstrate superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response after 1 dose of BNT162b2 OMI compared to after 1 dose of

BNT162b2 given as the fourth dose in participants without serological or virological evidence of past SARS CoV 2 infection up to 1 month after Dose 4. Results were reported as a GMR of the SARS CoV-2 50% neutralizing titers and the difference in percentages of participants with seroresponse, at 1 month after Dose 4, as described below.

Statistical methods

Superiority analyses:

GMR: The GMR was calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided 95% CIs were obtained by calculating CIs using Student's t-distribution for the mean difference on the logarithmically transformed assay results and exponentiating the confidence limits.

Superiority based on GMR was declared if the lower limit of the 2-sided 95% CI for the GMR is greater than >1.

The secondary objective of "super" superiority was evaluated using a 1.5-fold margin for GMR. "Super" superiority for GMR was established if the lower limit of the 2-sided 95% CI for the GMR is >1.5.

Noninferiority analyses:

Seroresponse: defined as achieving a ≥4-fold increase in SARS CoV-2 neutralizing titers over pre-booster (ie, pre-Dose 4) titers. The difference in percentages and the associated 2 sided 95% CI calculated using the Miettinen and Nurminen method were provided.

Noninferiority based on seroresponse rate was declared if the lower bound of the 2 sided 95% CI for the difference in seroresponse rate was greater than -5%.

Additional analyses:

GMT: calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% Cis will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits.

GMFR: calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2 sided 95% CIs will be obtained by constructing CIs using Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

Subgroup analyses of immunogenicity were conducted based on demographic characteristics (age, sex, race, ethnicity) and SARS-CoV-2 baseline status (positive or negative).

Analysis sets

Enrolled: All participants who have a signed ICD.

Randomized/assigned: All participants who are assigned a randomization number in the IWR system.

Evaluable immunogenicity: All eligible randomized/assigned participants who receive the first study intervention to which they are randomized (for Groups 1, 2b, 3, and 4) or receive 2 doses of study intervention to which they are randomized or assigned with Dose 2 received within 19 to 42 days after Dose 1 (for Groups 2 and 5), have a valid and determinate immunogenicity result from the blood sample collected within 28 to 42 days after the first study vaccination (for Groups 1, 2b, 3 and 4) or

within 28 to 42 days after the second study vaccination (for Groups 2 and 5), and have no other important protocol deviations as determined by the clinician.

All-available immunogenicity: All randomized/assigned participants who receive at least 1 dose of the study intervention with a valid and determinate immunogenicity result after vaccination.

Safety: All participants who receive at least 1 dose of the study intervention.

Multiplicity:

The 3 cohorts (2-dose BNT162b2-experienced, 3-dose BNT162b2-experienced, and COVID-19 vaccine–naïve individuals) are different populations with different objectives. The 3 populations are included in the same study to improve operational efficiency. Therefore, no type I error adjustments was applied to between the immunogenicity assessments of the 3 populations.

For Cohort 2 the objectives will be evaluated in sequential order as listed below using a 1-sided alpha of 0.025:

(G3vG4A) To demonstrate the superiority with respect to the level of neutralizing titers and the noninferiority with respect to the seroresponse rate of the anti-Omicron immune response after 1 dose of BNT162b2 OMI compared to after 1 dose of BNT162b2 given as the fourth dose in BNT162b2 experienced participants →

(G3vG4B) To demonstrate the "super" superiority of the anti-Omicron immune response after 1 dose of BNT162b2 OMI compared to after 1 dose of BNT162b2 given as the fourth dose in BNT162b2-experienced participants given as the fourth dose in BNT162b2-experienced participants

4.2.2 Results

Immunogenicity populations

Full expanded set

The subset of 60 participants across both vaccine groups that comprised the sentinel group was not included in the full expanded set (to which 580 participants were randomized; Table 6).

For the full expanded set, the evaluable immunogenicity population included 263 participants (92.6%) in the BNT162b2 OMI group and 280 participants (94.6%) in the BNT162b2 group. Exclusions from the evaluable immunogenicity population were generally balanced across vaccine groups; the most common reason for exclusion was participants not having at least 1 valid and determinate immunogenicity result within 28-42 days after first study (Dose 4) vaccination (3.4%).

For the full expanded set, the evaluable immunogenicity population for participants without evidence of infection prior to 1 month after Dose 4 included a total of 436 participants: 208 participants (73.2%) in the BNT162b2 OMI group and 228 participants (77.0%) in the BNT162b2 group.

Table 19. Immunogenicity Populations - Cohort 2 - Full Expanded Set

	Vaccine Group (as Randomized)		
	BNT162b2 OMI (30 µg) n[a] (%)	**BNT162b2 (30 µg) n[a] (%)**	**Total n[a] (%)**
Randomized[b]	284 (100.0)	296 (100.0)	580 (100.0)

All-available immunogenicity population	277 (97.5)	290 (98.0)	567 (97.8)
Excluded from all-available immunogenicity population	7 (2.5)	6 (2.0)	13 (2.2)
Reason for exclusion			
Did not have at least 1 valid and determinate immunogenicity result after study vaccination	7 (2.5)	6 (2.0)	13 (2.2)
Evaluable immunogenicity population	263 (92.6)	280 (94.6)	543 (93.6)
Participants without evidence of infection up to 1 month after the first study vaccination[c]	208 (73.2)	228 (77.0)	436 (75.2)
Excluded from evaluable immunogenicity population	21 (7.4)	16 (5.4)	37 (6.4)
Reason for exclusion[d]			
Did not meet eligibility and randomization criteria	10 (3.5)	8 (2.7)	18 (3.1)
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after the first study vaccination	12 (4.2)	8 (2.7)	20 (3.4)
Had important protocol deviation	9 (3.2)	8 (2.7)	17 (2.9)

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

Note: Full expanded set = Cohort 2 excluding the sentinel group.

[a] n = Number of participants with the specified characteristic, or the total sample.

[b] These values are the denominators for the percentage calculations.

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

[d] Participants may have been excluded for more than 1 reason.

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Baseline data

Primary Immunogenicity Subset

The primary immunogenicity subset comprised a random sampling of 175 participants from each vaccine group selected from the full expanded set.

For the primary immunogenicity subset, the evaluable immunogenicity population included 168 participants (96.0%) each in the BNT162b2 OMI and BNT162b2 groups. Exclusions from the evaluable immunogenicity population were balanced across vaccine groups; the most common reason for exclusion was participants did not meet eligibility and randomization criteria (3.4%), which occurred in 2.9% of BNT162b2 OMI participants vs 4.0% of BNT162b2 recipients.

For the primary immunogenicity subset, the evaluable immunogenicity population for participants without evidence of infection prior to 1 month post-Dose 4 included a total of 273 participants: 132 participants (75.4%) in the BNT162b2 OMI group and 141 participants (80.6%) in the BNT162b2 group.

Table 20. Immunogenicity Populations – Cohort 2 – Primary Immunogenicity Subset

	Vaccine Group (as Randomized)		
	BNT162b2 OMI (30 µg) n[a] (%)	BNT162b2 (30 µg) n[a] (%)	Total n[a] (%)
Randomized[b]	175 (100.0)	175 (100.0)	350 (100.0)
All-available immunogenicity population	175 (100.0)	175 (100.0)	350 (100.0)
Evaluable immunogenicity population	168 (96.0)	168 (96.0)	336 (96.0)
Participants without evidence of infection up to 1 month after the first study vaccination[c]	132 (75.4)	141 (80.6)	273 (78.0)
Excluded from evaluable immunogenicity population	7 (4.0)	7 (4.0)	14 (4.0)
Reason for exclusion[d]			
Did not meet eligibility and randomization criteria	5 (2.9)	7 (4.0)	12 (3.4)
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after the first study vaccination	2 (1.1)	0	2 (0.6)
Had important protocol deviation	4 (2.3)	7 (4.0)	11 (3.1)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Primary immunogenicity subset = a random sample of 175 participants in each vaccine group selected from the full expanded set.
a. n = Number of participants with the specified characteristic, or the total sample.
b. These values are the denominators for the percentage calculations.
c. Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
d. Participants may have been excluded for more than 1 reason.
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(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File:

Full expanded set

For the full expanded set, demographics of participants without evidence of infection prior to 1 month post-Dose 4 (N=436) in the evaluable immunogenicity population were similar in the BNT162b2 OMI and BNT162b2 groups (Table 21). This analysis population had similar demographics compared to the safety population.

Most participants were White (73.9%), with 15.6% Asian participants, 5.0% Black or African American participants, 3.4% multiracial participants, and other racial groups comprising <1% each. There were 13.8% Hispanic/Latino participants. The median age at the time of study vaccination was 44 years, and 53.2% of participants were male. All (100%) study participants were enrolled in the US.

Obese participants made up 37.8% of this analysis population. The median time from the first booster dose of BNT162b2 (received prior to C4591031 Substudy D) was 3.9 months.

For the full expanded set, demographic characteristics for participants with or without evidence of infection prior to 1 month after first study (Dose 4) vaccination (evaluable immunogenicity

population) and the all-available immunogenicity population were also similar to those in the safety population.

Table 21. Demographic Characteristics - Cohort 2 - Full Expanded Set - Participants Without Evidence of Infection up to 1 Month After First Study Vaccination - Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)		
	BNT162b2 OMI (30 µg) (N[a]=208) n[b] (%)	**BNT162b2 (30 µg) (N[a]=228) n[b] (%)**	**Total (N[a]=436) n[b] (%)**
Sex			
Male	111 (53.4)	121 (53.1)	232 (53.2)
Female	97 (46.6)	107 (46.9)	204 (46.8)
Race			
White	158 (76.0)	164 (71.9)	322 (73.9)
Black or African American	10 (4.8)	12 (5.3)	22 (5.0)
American Indian or Alaska Native	1 (0.5)	3 (1.3)	4 (0.9)
Asian	30 (14.4)	38 (16.7)	68 (15.6)
Native Hawaiian or other Pacific Islander	2 (1.0)	1 (0.4)	3 (0.7)
Multiracial	6 (2.9)	9 (3.9)	15 (3.4)
Not reported	1 (0.5)	1 (0.4)	2 (0.5)
Ethnicity			
Hispanic/Latino	32 (15.4)	28 (12.3)	60 (13.8)
Non-Hispanic/non-Latino	176 (84.6)	200 (87.7)	376 (86.2)
Country			
USA	208 (100.0)	228 (100.0)	436 (100.0)
Age group (at first study vaccination)			
18-30 Years	27 (13.0)	31 (13.6)	58 (13.3)
31-55 Years	181 (87.0)	197 (86.4)	378 (86.7)
Age at first study vaccination (years)			
Mean (SD)	42.1 (9.21)	42.6 (8.95)	42.4 (9.07)
Median	44.0	44.5	44.0
Min, max	(18, 55)	(19, 55)	(18, 55)
Time (months) from Dose 3 of BNT162b2 (received prior to the study) to first study vaccination			
N	208	228	436
Mean (SD)	4.2 (0.92)	4.2 (0.93)	4.2 (0.92)
Median	3.9	3.9	3.9
Min, max	(3.3, 6.5)	(3.3, 6.5)	(3.3, 6.5)
<3 Months	0	0	0
3 to <4 Months	110 (52.9)	124 (54.4)	234 (53.7)
4 to <5 Months	71 (34.1)	72 (31.6)	143 (32.8)
5 to <6 Months	0	0	0
≥6 Months	27 (13.0)	32 (14.0)	59 (13.5)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	4 (1.9)	2 (0.9)	6 (1.4)
Normal weight (≥18.5-24.9 kg/m^2)	57 (27.4)	68 (29.8)	125 (28.7)

Overweight (≥25.0-29.9 kg/m^2)	59 (28.4)	81 (35.5)	140 (32.1)
Obese (≥30.0 kg/m^2)	88 (42.3)	77 (33.8)	165 (37.8)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis. Note: Full expanded set = Cohort 2 excluding the sentinel group.
[a]N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b]n = Number of participants with the specified characteristic.
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Primary Immunogenicity Analyses – Primary Immunogenicity Subset

Superiority Analysis - GMR of Omicron-Neutralizing Titers in BNT162b2 OMI Dose 4 Recipients Compared to BNT162b2 Dose 4 Recipients

In the primary immunogenicity subset of participants without prior evidence of infection up to 1 month after first study (Dose 4) vaccination, the ratio of GMTs for the BNT162b2 OMI group to BNT162b2 group (GMR) was 1.75 (2-sided 95% CI: 1.39, 2.22) (Table 22).

The lower bound of the 2-sided 95% CI for GMR was >1, which meets the prespecified simple superiority criterion. Therefore, simple superiority of BNT162b2 OMI to BNT162b2 for the Omicron variant was achieved based on GMR at 1 month after Dose 4.

Table 22. Geometric Mean Ratios For Between Vaccine Group Comparison - Cohort 2 - Primary Immunogenicity Subset - Participants Without Evidence of Infection up to 1 Month After First Study Vaccination - Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)				
		BNT162b2 OMI (30 µg)		BNT162b2 (30 µg)		BNT162b2 OMI (30 µg)/ BNT162b2 (30 µg)
Assay	**Dose/Sampling Time Point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**	**GMR[d] (95% CI[d])**
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	1/1 Month	132	1929.2 (1631.5, 2281.1)	141	1099.6 (932.0, 1297.4)	1.75 (1.39, 2.22)

Abbreviations: GMT = geometric mean titer; GMR = geometric mean ratio; 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: Primary immunogenicity subset = a random sample of 175 participants in each vaccine group selected from the full expanded set.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first 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 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] GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (BNT162b2 OMI [30 µg] - BNT162b2 [30 µg]) and the corresponding CI (based on the Student t distribution).

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./nda2_ubd/C4591031_D/adva_s001_gmr_pri_inf_eval

Noninferiority Analysis - Difference in Seroresponse Rates to Omicron Variant in BNT162b2 OMI Dose 4 Recipients Compared to BNT162b2 Dose 4 Recipients

In the primary immunogenicity subset of participants without prior evidence of infection up to 1 month after first study (Dose 4) vaccination, 62.3% of participants in the BNT162b2 OMI group and 39.3% of participants in the BNT162b2 group achieved seroresponse to Omicron variant at 1 month after the study vaccination. The difference in proportions of participants who achieved seroresponse to Omicron variant between the 2 vaccine groups was 23.0% (2-sided 95% CI: 11.1%, 34.3%) (Table 23).

Noninferiority of BNT162b2 OMI to BNT162b2 for the Omicron variant was achieved based on seroresponse rates at 1 month after Dose 4. The lower bound of the 2-sided 95% CI was greater than 0%, suggesting higher seroresponse to Omicron variant in BNT162b2 OMI recipients than BNT162b2 recipients.

Table 23. Difference in Percentages of Participants With Seroresponse - Cohort 2 - Primary Immunogenicity Subset - Participants Without Evidence of Infection up to 1 Month After First Study Vaccination - Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)				
		BNT162b2 OMI (30 µg)		BNT162b2 (30 µg)		Difference
Assay	Dose/Sampling Time Point	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.1 - NT50 (titer)	1/1 Month	130	81 (62.3) (53.4, 70.7)	140	55 (39.3) (31.1, 47.9)	23.0 (11.1,34.3)

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: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
Note: Primary immunogenicity subset = a random sample of 175 participants in each vaccine group selected from the full expanded set.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first study vaccination blood sample collection)
and had no medical history of COVID-19 were included in the analysis.

[a] N = number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculations.

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

[c] Exact 2-sided CI based on the Clopper and Pearson method.

[d] Difference in proportions, expressed as a percentage (BNT162b2 OMI [30 µg] - BNT162b2 [30 µg]).

[e] 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage. PFIZER CONFIDENTIAL SDTM Creation: 06MAY2022 (08:21) Source Data: adva Table Generation: 18MAY2022 (06:47) (Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File:./nda2_ubd/C4591031_D/adva_s001_diff_pri_inf_eval

Secondary Immunogenicity Analysis – Primary Immunogenicity Subset

"Super" Superiority Analysis – GMR of Omicron-Neutralizing Titers in BNT162b2 OMI Dose 4 Recipients Compared to BNT162b2 Dose 4 Recipients

As shown in Table 10 for the superiority analysis, in the primary immunogenicity subset of participants without prior evidence of infection up to 1 month after first study (Dose 4). vaccination, the GMR (BNT162b2 OMI / BNT162b2) was 1.75 (2-sided 95% CI: 1.39, 2.22).

As the lower bound of the 2-sided 95% CI for GMR was not >1.5, "super" superiority of BNT162b2 OMI to BNT162b2 for the Omicron variant was not achieved based on the prespecified criterion.

Descriptive Immunogenicity Analyses – Full Expanded Set

The full expanded set comprised Cohort 2 participants excluding the 60 participants across both vaccine groups included in the sentinel group.

Immunogenicity evaluations presented for the full expanded set include descriptive summary of immune response to Omicron variant and reference strain for each vaccine group and post hoc analyses of GMR and difference in seroresponse between the 2 vaccine groups, corresponding to the primary immunogenicity analyses in the primary immunogenicity subset.

GMR of Omicron-Neutralizing Titers in BNT162b2 OMI Dose 4 Recipients Compared to BNT162b2 Dose 4 Recipients

In the full expanded set of participants without prior evidence of infection up to 1 month after first study (Dose 4) vaccination, the post hoc analysis of the ratio of GMTs for the BNT162b2 OMI group to BNT162b2 group (GMR) was 1.96 (2-sided 95% CI: 1.62, 2.37) (Table 24), consistent with the results in the primary immunogenicity subset in which the simple superiority criterion (lower bound of the 2-sided 95% CI >1) was met. Furthermore, this would meet the "super" superiority criterion (lower bound of the 2-sided 95% CI >1.5).

Table 24. Geometric Mean Ratios For Between Vaccine Group Comparison - Cohort 2 - Full Expanded Set - Participants Without Evidence of Infection up to 1 Month After First Study Vaccination - Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)				
		BNT162b2 OMI (30 µg)		BNT162b2 (30 µg)		BNT162b2 OMI (30 µg)/ BNT162b2 (30 µg)
Assay	Dose/Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])
SARS-CoV-2 neutralization assay- Omicron BA.1 - NT50 (titer)	1/1 Month	208	2086.7 (1812.7, 2402.0)	228	1063.2 (935.8, 1207.9)	1.96 (1.62, 2.37)

Abbreviations: GMT = geometric mean titer; GMR = geometric mean ratio; 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: Full expanded set = Cohort 2 excluding the sentinel group.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first 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 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] GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (BNT162b2 OMI [30 µg] - BNT162b2 [30 µg]) and the corresponding CI (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 06MAY2022 (08:21) Source Data: adva Table Generation: 18MAY2022 (01:57) (Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File: ./nda2_ubd/C4591031_D/adva_s001_gmr_inf_eval

Difference in Seroresponse Rates to Omicron Variant in BNT162b2 OMI Dose 4 Recipients Compared to BNT162b2 Dose 4 Recipients

In the full expanded set of participants without prior evidence of infection up to 1 month after first study (Dose 4) vaccination, the post hoc analysis of the difference in proportions of participants who achieved seroresponse between the BNT162b2 OMI and BNT162b2 groups was 21.4% (2-sided 95%

CI: 12.0%, 30.4%) (Table 25), similar to the results in the primary immunogenicity subset in which the noninferiority criterion (lower bound of the 2-sided 95% CI >-5%) was achieved.

Table 25. Difference in Percentages of Participants With Seroresponse - Cohort 2 - Full Expanded Set - Participants Without Evidence of Infection up to 1 Month After First Study Vaccination - Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)				
		BNT162b2 OMI (30 µg)		BNT162b2 (30 µg)		Difference
Assay	Dose/Sampling Time Point	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.1 - NT50 (titer)	1/1 Month	206	127 (61.7) (54.6, 68.3)	226	91 (40.3) (33.8, 47.0)	21.4 (12.0, 30.4)

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: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
Note: Full expanded set = Cohort 2 excluding the sentinel group.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
[a] N = number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculations.
[b] n = Number of participants with seroresponse for the given assay at the given sampling time point.
[c] Exact 2-sided CI based on the Clopper and Pearson method.
[d] Difference in proportions, expressed as a percentage (BNT162b2 OMI [30 µg] - BNT162b2 [30 µg]).
[e] 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
PFIZER CONFIDENTIAL SDTM Creation: 06MAY2022 (08:21) Source Data: adva Table Generation: 18MAY2022 (01:57) (Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File: ./nda2_ubd/C4591031_D/adva_s001_diff_inf_eval

GMTs for Omicron Variant and Reference Strain

In the full expanded set of participants without prior evidence of infection up to 1 month after first study (Dose 4) vaccination, for both the BNT162b2 OMI and BNT162b2 groups there was a substantial increase in SARS-CoV-2 50% neutralizing GMTs for the Omicron (BA.1) variant and reference strains at 1 month post-Dose 4 compared to the pre-vaccination baseline (Table 26, Figure 1, Figure 2).

At 1 month post-Dose 4, for the Omicron variant, GMTs were higher for the BNT162b2 OMI group (2086.7; 2-sided 95% CI: 1812.7, 2402.0) than the BNT162b2 group (1063.2; 2-sided 95% CI: 935.8, 1207.9) (Table 24). For the reference strain, GMTs were similar for the BNT162b2 OMI and BNT162b2 groups.

Table 26. Geometric Mean Titers - Cohort 2 - Full Expanded Set - Participants Without Evidence of Infection up to 1 Month After First Study Vaccination - Evaluable Immunogenicity Population

Assay	Dose/Sampling Time Point[a]	Vaccine Group (as Randomized) BNT162b2 OMI (30 µg) n[b]	BNT162b2 OMI (30 µg) GMT[c] (95% CI[c])	BNT162b2 (30 µg) n[b]	BNT162b2 (30 µg) GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	1/Prevax	206	374.1 (315.8, 443.2)	226	315.0 (269.0, 368.9)
	1/1 Month	208	2086.7 (1812.7, 2402.0)	228	1063.2 (935.8, 1207.9)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	1/Prevax	205	4430.2 (3852.0, 5095.3)	226	3999.0 (3529.5, 4531.0)
	1/1 Month	207	11997.1 (10553.5, 13638.3)	227	12009.9 (10744.3, 13424.6)

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: Full expanded set = Cohort 2 excluding the sentinel group.

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

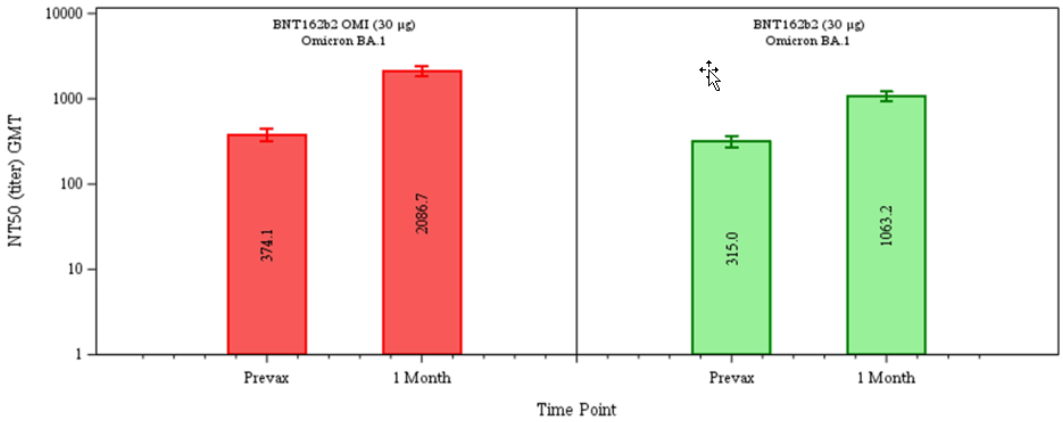
[a] Protocol-specified timing for blood sample collection.

[b] n = Number of participants with valid and determinate assay results for the specified assay at 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.

PFIZER CONFIDENTIAL SDTM Creation: 06MAY2022 (08:21) Source Data: adva Table Generation: 18MAY2022 (01:57) (Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File: ./nda2_ubd/C4591031_D/adva_s001_gmt_inf_eval

Figure 1. Geometric Mean Titers and 95% CIs: SARS-CoV-2 Neutralization Assay – NT50 – Omicron Variant – Cohort 2 – Full Expanded Set – Participants Without Evidence of Infection up to 1 Month After First Study Vaccination – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; 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.

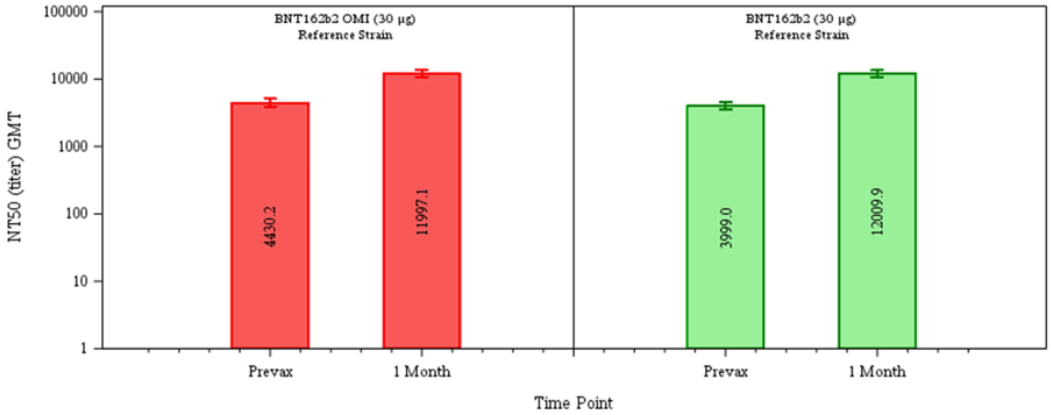
Note: Full expanded set = Cohort 2 excluding the sentinel group.

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

Note: Number within each bar denotes geometric mean.

PFIZER CONFIDENTIAL SDTM Creation: 06MAY2022 (08:21) Source Data: adva Table Generation: 24MAY2022 (22:59) (Cutoff Date: 11MAR2022, Snapshot Date: 8APR2022) Output File: ./nda2 ubd/C4591031 D/adva f002 om gmt

Figure 2. Geometric Mean Titers and 95% CIs: SARS-CoV-2 Neutralization Assay – NT50 – Reference Strain – Cohort 2 – Full Expanded Set – Participants Without Evidence of Infection up to 1 Month After First Study Vaccination – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; 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: Full expanded set = Cohort 2 excluding the sentinel group.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 06MAY2022 (08:21) Source Data: adva Table Generation: 24MAY2022 (22:59)
(Cutoff Date: 11MAR2022, Snapshot Date: 8APR2022) Output File: ./nda2 ubd/C4591031 D/adva f002 wt gmt

GMFRs for Omicron Variant and Reference Strain

In the full expanded set of participants without prior evidence of infection up to 1 month after first study (Dose 4) vaccination, the GMFRs from Dose 4 to 1 month post-Dose 4 for the Omicron variant were higher for the BNT162b2 OMI group (5.6; 2-sided 95% CI: 4.9, 6.4) than the BNT162b2 group (3.4; 2-sided 95% CI: 3.0, 3.8) (Table 27). For the reference strain, the GMFRs were similar for the 2 groups, and similar to the BNT162b2 group GMFRs for the Omicron variant.

Table 27. Geometric Mean Fold Rises From Before First Study Vaccination to Each Subsequent Time Point - Cohort 2 - Full Expanded Set - Participants Without Evidence of Infection up to 1 Month After First Study Vaccination - Evaluable Immunogenicity Population

Assay	Dose/Sampling Time Point[a]	Vaccine Group (as Randomized)			
		BNT162b2 OMI (30 µg)		BNT162b2 (30 µg)	
		n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	1/1 Month	206	5.6 (4.9, 6.4)	226	3.4 (3.0, 3.8)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	1/1 Month	204	2.7 (2.4, 3.0)	225	3.0 (2.7, 3.3)

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: Full expanded set = Cohort 2 excluding the sentinel group.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first 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 prevaccination 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 SDTM Creation: 06MAY2022 (08:21) Source Data: adva Table Generation: 18MAY2022 (01:58) (Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File: ./nda2_ubd/C4591031_D/adva_s001_gmfr_inf_eval

Subgroup Analyses

Overall, for all BNT162b2 and BNT162b2 OMI recipients, there were no clinically meaningful differences between subgroups for neutralizing GMTs and seroresponse rates, for the Omicron variant except for baseline SARS-CoV-2 status. As several subgroups (eg, younger age group, Black or African American, Asian, Hispanic/Latino, SARS-CoV-2 baseline positive or NAAT positive participants) included a limited number of participants, their results should be interpreted with caution.

- GMTs at 1-month post-Dose 4 for both BNT162b2 OMI and BNT162b2 recipients were generally higher for participants who were baseline positive and the subset of those who were NAAT positive at baseline which, in light of the study timeframe, can be inferred to be an Omicron infection, compared to those who were baseline negative for SARS-CoV-2.
- GMFRs for both BNT162b2 OMI and BNT162b2 recipients were generally higher for the participants in the subgroup for baseline positive by NAAT compared to those for participants who were baseline positive and baseline negative for SARS-CoV-2.
- Seroresponse rates at 1-month post-Dose 4 for both BNT162b2 OMI and BNT162b2 recipients were generally higher for participants who were NAAT positive at baseline compared to those who were baseline positive or baseline negative for both Omicron variant and reference strain.

Immunogenicity conclusions of Substudy D

Overall, for the primary and secondary immunogenicity analyses for the Omicron variant, BNT162b2 OMI 30 µg met the pre-specified criteria for simple superiority with respect to GMR and noninferiority with respect to seroresponse rate when compared to BNT162b2 30 µg when administered as a fourth dose.

Primary Immunogenicity Analyses - Superiority and Noninferiority – Primary Immunogenicity Subset

In participants without prior evidence of infection up to 1 month after Dose 4, for the Omicron (BA.1) variant:

- The ratio of GMTs for the BNT162b2 OMI group to BNT162b2 group (GMR) was 1.75 (2-sided 95% CI: 1.39, 2.22). As the lower bound of the 2-sided 95% CI for GMR was >1, the simple superiority of BNT162b2 OMI to BNT162b2 for the Omicron variant was achieved based on GMR at 1 month after Dose 4.
- Seroresponse rates to the Omicron variant were 62.3% in the BNT162b2 OMI group and 39.3% in the BNT162b2 group, and the difference in proportions of participants who achieved seroresponse to Omicron variant between the BNT162b2 OMI and BNT162b2 groups was 23.0% (2-sided 95% CI: 11.1%, 34.3%). As the lower bound of the 2-sided 95% CI for GMR was greater than the prespecified margin of -5%, noninferiority of BNT162b2 OMI to BNT162b2 for the Omicron variant was achieved based on seroresponse rates at 1 month after Dose 4. The lower bound of the 2-sided 95% CI was greater than 0%, suggesting higher seroresponse to Omicron variant in BNT162b2 OMI recipients than BNT162b2 recipients.

Secondary Immunogenicity Analysis – "Super" Superiority – Primary Immunogenicity Subset
As shown for the superiority analysis, in the primary immunogenicity subset of participants without prior evidence of infection up to 1 month after Dose 4, the GMR (BNT162b2 OMI / BNT162b2) was 1.75 (2-sided 95% CI: 1.39, 2.22). As the lower bound of the 2-sided 95% CI for GMR was not >1.5, "super" superiority of BNT162b2 OMI to BNT162b2 for the Omicron variant was not achieved at 1 month after Dose 4 based on the prespecified criterion.

Descriptive Immunogenicity Analyses – Full Expanded Set
Overall, immune responses to the Omicron variant and reference strain were elicited by BNT162b2 OMI and BNT162b2 in the full expanded set; descriptive analyses for the Omicron variant were consistent with those in the primary immunogenicity subset. For both groups, analyses by age, sex, race, and ethnicity suggested no clinically meaningful differences between subgroups. For the Omicron variant and reference strains, for both vaccine groups the immune responses up to 1 month after Dose 4 (GMTs, GMFRs, seroresponse rates) were generally higher for participants with baseline positive SARS-CoV-2 status compared to those with baseline negative status.

In participants without prior evidence of infection up to 1 month after Dose 4:

- The ratio of GMTs for the BNT162b2 OMI group to BNT162b2 group (GMR) for the Omicron variant was 1.96 (2-sided 95% CI: 1.62, 2.37), consistent with the results in the primary immunogenicity subset in which the simple superiority criterion (lower bound of the 2-sided 95% CI >1) was met. Furthermore, this would meet the "super" superiority criterion (lower bound of the 2-sided 95% CI >1.5).
- The difference in proportions of participants who achieved seroresponse to the Omicron variant between the BNT162b2 OMI and BNT162b2 groups was 21.4% (2-sided 95% CI: 12.0%, 30.4%), similar to the results in the primary immunogenicity subset in which the noninferiority criterion (lower bound of the 2 sided 95% CI >-5%) was achieved.

For both the BNT162b2 OMI and BNT162b2 groups, there was a substantial increase in SARS-CoV-2 50% neutralizing GMTs for the Omicron variant and reference strains at 1 month post-Dose 4 compared to the pre-vaccination baseline. For the Omicron variant GMTs were higher for the BNT162b2 OMI group (2086.7; 2-sided 95% CI: 1812.7, 2402.0) than the BNT162b2 group (1063.2; 2-sided 95% CI: 935.8, 1207.9).

The GMFRs from Dose 4 to 1 month post-Dose 4 for the Omicron variant were higher for the BNT162b2 OMI group (5.6; 2-sided 95% CI: 4.9, 6.4) than the BNT162b2 group (3.4; 2-sided 95% CI: 3.0, 3.8).

The proportion of participants who achieved seroresponse in SARS-CoV-2 50% neutralizing titers at 1 month post-Dose 4 for the Omicron variant was 61.7% (2-sided 95% CI: 54.6%, 68.3%) for the BNT162b2 OMI group and 40.3% (2-sided 95%CI: 33.8%, 47.0%) for the BNT162b2 group.

4.3 Immunogenicity Discussion

Background

The SARS-CoV-2 virus has repeatedly evolved and mutated, originating several variants and causing new waves of infection. The variants have so far shown cross-reactivity with the original strain, which was the base for the currently approved vaccines. However, there is a concern that presently circulating virus variants are less cross-reactive with the original strain. The variant causing the latest waves of disease has been the Omicron variant, with several subvariants beginning with BA.1 and currently BA.5 being the most dominant in the EU. It is hypothesised that a booster vaccine based on a

variant virus strain will result in broader immunity against SARS-CoV-2. In order to optimize vaccines, regulatory bodies (e.g. ICMRA) and the WHO have suggested that a bivalent vaccine including both original as well as an omicron variant may be desirable.

The MAH has conducted clinical studies with variant vaccine mono- and bivalent (Original/Omicron BA.1) candidates including the mRNA transcribing Omicron variant S protein.

This application concerns a booster dose with a bivalent original/Omicron (BA.1) vaccine, (BNT162b2 Original 15 µg + BNT162b2 OMI 15 µg = "Original/Omicron BA.1" 15/15 µg), given ≥4 months after the third dose to subjects≥12 years of age.

Clinical studies

The application is based primarily on clinical data from Study C4591031 Substudy E, investigating the safety, tolerability, and immune responses of a fourth dose of bivalent vaccine (subjects had previously received three doses of the Original Comirnaty) in approximately 1840 older adult (>55 years of age) participants. Original/Omicron BA.1 15/15µg (30 µg) was compared to Original/Omicron BA.1 at 60 µg; to monovalent Omicron BA.1 at 30 and 60 µg; and to monovalent Original at 30 and 60 µg.

Supportive data are provided from Study C4591031 Substudy D investigating safety and immunogenicity of an investigational monovalent Omicron BA.1 vaccine where 640 subjects aged 18-55 years (majority 30-55 years, 13% were 18-<30 years old) were randomized to receive either the monovalent Omicron BA.1 30µg (n=315) or the authorized Original 30µg (n=325) as a fourth dose. In this substudy also all subjects had previously received three doses of Original Comirnaty 30 µg.

Both substudies had as its primary objective the investigation of the immunogenicity of different Omicron containing vaccine formulations as a fourth dose compared to a fourth dose of Original Comirnaty 30 µg.

The primary endpoint of these studies was to show that the novel vaccine formulations, containing the Omicron strain, can induce superior immune responses to the Omicron BA.1 virus variant, and induce non-inferior response to the reference strain compared to Original Comirnaty 30 µg.

There is currently no immunological correlate of protection established for COVID-19, and therefore the relevance of numerical titre differences, in terms of impact on protection against severe disease or any clinical disease, cannot be determined.

The serological comparison is considered acceptable as efficacy has been demonstrated in clinical studies and neutralizing antibodies are considered an acceptable surrogate endpoint for efficacy. As stated above, it is assumed that efficacy against a new variant will be at least comparable and possibly superior, if superior levels of neutralizing antibodies are detected following booster with a variant vaccine compared to the original vaccine. The quantification of such incremental effects, however, will need to be based on real-world evidence, given that no randomised controlled trial of the variant-adapted vaccine against the original vaccine is required, according to regulatory policy (ICMRA).

Substudy E contained 6 study arms. In each arm approximately 230 individuals received either:

1) BNT162b2 (Original) 30 µg

2) BNT162b2 (Original) 60 µg

3) BNT162b2 OMI (Omicron BA.1) 30 µg

4) BNT162b2 OMI (Omicron BA.1) 60 µg

5) bivalent BNT162b2 15 µg + BNT162b2 OMI 15 µg (Original/(Omicron BA.1) 15/15 µg)

6) bivalent BNT162b2 30 µg + BNT162b2 OMI 30 µg. (Original/(Omicron BA.1) 30/30 µg)

The fourth dose was given median 6.3 months (4.7-12.9) from the third dose. Blood samples for immunogenicity evaluations were collected on the vaccination day (baseline) and 1 month after fourth dose.

For substudy D, results have been reported for two study interventions with monovalent vaccines: original 30 µg and Omicron BA.1 30 µg

The immunogenicity results for expanded cohort analyses were based on validated assays for 50% SARS-CoV-2 neutralizing titers on a newly developed 384-well assay platform (reference strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.1) reported as GMTs, GMRs, percentages/difference in percentages with seroresponse, GMFRs. Of note, the 384-well SARS-CoV-2 neutralization assays have been recently validated and, unlike the previously used validated 96-well mNeonGreen SARS-CoV-2 neutralization assay platform, do not use reporter viruses with fluorescent markers. The neutralizing titers in the 384-well platform and 96-well platform are not comparable; the titers from the 384-well assay platform are approximately 2.5-fold higher than those from the 96-well assay platform. During the RR, questions about the novel serology method was asked and the MAH has answered satisfactorily.

Neutralization of Omicron variant BA4/BA5 was not studied using this validated assay but in a smaller study population including 100 individuals in both Original/Omicron BA.1 15/15 µg and Original 30µg using unvalidated method FFRNT.

The majority (80%) of the study population did not have signs of previous SARS-COV-2 infection. The majority of participants had high levels of antibodies against the reference strain (GMT ca 1400) at baseline and also low, but detectable levels of anti-Omicron antibodies at baseline (GMT ca 70).

In Substudy E superior immune responses (lower limit of the 2-sided 95% CI for the Geometric Mean Ratio (GMR) is >1) to the Omicron BA.1 strain was demonstrated for all 4 novel Omicron strain containing vaccine formulations in comparison to the approved Comirnaty 30 µg 1 month after fourth dose. The GMR for Original/Omicron BA.1 15/15 µg vs. the approved Original 30 µg was 1.56 (95% CI 1.17, 2.08). Compared to the pre-boost titre, the antibody titre against Omicron BA.1 strain increased 9.1 (7.3,11.2) fold after bivalent Original/(Omicron BA.1) 15/15 µg vaccine and 5.8 (4.6, 7.2) fold after Original 30 µg vaccine.

The seroresponse rate against the Omicron BA.1 strain, for Original/Omicron BA.1 30µg was 71.6 % versus 57 % for Original 30µg, demonstrating statistically significant superiority (difference 14.6 % (4.0, 24.9), pre-defined criteria >-5%).

Noninferiority based on the GMR for the reference Wuhan strain response was met by both bivalent vaccine groups as the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion). The GMR for Original/Omicron BA.1 30 µg vs. the approved Original 30 µg was 0.99 (0.82, 1.2). Compared to pre-boost titres, the antibody titer against reference Strain increased 4.3 fold after both vaccines.

The seroresponse rate for Original/Omicron BA.1 30 µg against the reference strain was 50 %, versus 49.2% for Original 30µg.

All study arms had about 230 individuals and a short follow up, which is too low to evaluate VE against COVID-19. Breakthrough infections, presumably due to BA.1 or BA.2, were seen in all study arms. There is no statistical basis to infer different efficacy between variant vaccines.

Additional descriptive analyses from Substudy E were performed to further characterize BA.4/BA.5 neutralization responses following a booster (fourth) dose. A total of 100 participants were randomly

selected from each vaccine group in the expanded cohort. Demographic characteristics for participants in this subset were similar between the two vaccine groups. The observed Omicron BA.4/BA.5 neutralizing GMTs at 1 month post-Dose were numerically slightly higher for the bivalent Original/Omicron BA.1 30 µg group compared to Original 30 µg group (167.4 vs 155.1). Overall, GMFRs (4.5 vs 3.3) and seroresponse (56% vs 42%) followed this trend. The data on immunogenicity against BA.5. were obtained with non-validated FFRNT assay. Moreover, it is not known if the numerically small increase in neutralising titres compared to that of the original product will be associated with improved relative efficacy.

Also, immunological response to Omicron BA.2.75 strain was investigated in 30 randomly selected individuals from both Original/Omicron BA.1 15/15 µg and Original arms from Substudy E. Overall, the observed Omicron BA.2.75 neutralizing GMTs at 1 month post-Dose in participants without evidence of infection were numerically slightly higher for the bivalent Original/Omicron BA.1 15/15 µg group compared to Original group (108.0 vs 88.8).

In substudy D approximately 640 participants ≥18 to ≤55 years of age received a fourth dose of either approved Original 30 µg or monovalent Omicron BA.1 30 µg about 4 month after the third dose. Superior immunogenicity to Omicron BA.1 and non-inferior response to reference strain were demonstrated for Omicron BA.1 30 µg compared to the original 30 µg vaccine.

Numerically, the highest GMR against Omicron BA.1 was achieved for the monovalent Omicron BA.1 60 µg vaccine candidate and the lowest GMR for the bivalent Original/Omicron BA.1 15/15 µg variant. This is as expected, since the magnitude of the immune response depends on the dose. Interestingly, Comirnaty 60 µg elicited numerically the same level of anti- Omicron antibodies as bivalent 15/15 µg, which indicates an ability of Comirnaty to elicit cross-neutralizing antibodies.

If the immune memory after primary series is established, the boosting dose can be lower than was used in primary series to trigger anamnestic response. Currently, the MAH seeks approval for bivalent 15/15 µg formulation as a booster dose and not as primary series, which has not been studied. Therefore, choosing the smallest effective dose is endorsed; moreover, an extrapolation of safety to younger adults would not be possible if the total dose is higher than 30 µg.

It is unknown to what extent the increase in neutralising titres against BA.1 would translate into increased protection against severe disease; against clinical disease; or against transmission, compared to the presently approved vaccine.

Immune responses are generally stronger in younger people compared to older. Therefore, one can extrapolate that the booster effect of Original/Omicron BA.1 30 µg against the Omicron BA.1 strain will be seen also in younger people, although data are only available from the abovementioned substudy D. In this study a monovalent Omicron BA.1 vaccine at 30 µg elicited stronger responses against Omicron BA.1, compared to the Original 30 µg. Whether the relative numerical increment in efficacy of Original/Omicron BA.1 compared to Original will be seen also for adults younger than 55, however, is unknown. These considerations are relevant also for adolescents 12-18 years of age.

No information about antibody kinetics over time after the fourth dose has been submitted.

The MAH seeks approval of a bivalent vaccine Original/Omicron BA.1 15/15 µg as a booster dose, i.e. third or fourth dose after a two-dose primary series, although the current application is based on data for a fourth dose. However, it is not anticipated that the use of the bivalent adapted vaccine instead of the monovalent original vaccine for a third dose would be in any way inferior. It can also be anticipated that the bivalent adapted vaccine could be used for boosting regardless of the number of previous doses, once the primary vaccination course has been given.

In conclusion, the CHMP is of the view that the submitted data support the use of bivalent

original/Omicron BA.1 15/15 µg as booster dose, as the immune responses against BA.1 were superior for the bivalent adapted vaccine compared to the original vaccine and the immune responses to the original reference strain were non-inferior.

5. Clinical Safety aspects

5.1 Methods

C4591031 Substudy E

Study design

C4591031 substudy E is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of monovalent BNT162b2 "Original" (30 and 60 µg), monovalent Omicron BA.1 "BA.1" (30 and 60 µg), and bivalent combination of Original and BA.1 (15/15µg and 30/30µg), given as a single fourth dose. Subjects were enrolled at investigator sites in the US only. Participants >55 years of age were randomized at a ratio of 1:1:1:1:1:1 to receive one of the study vaccines as a fourth dose.

Initially, for participants >55 years of age, sentinel cohorts (sponsor open label) of 20 participants per group were enrolled, followed by an expanded cohort. E-diary data from Day 1 and Day 2 for the first 30 participants enrolled in the sentinel cohort (5 per group) were evaluated prior to enrolment of the remaining 90 sentinel-cohort participants. This report presents interim data only for participants >55 years of age.

If, at any time, a participant develops acute respiratory illness, for the purposes of the study, he or she will be considered to potentially have COVID-19 illness. In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include collection of a nasal (midturbinate) swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid Xpert Xpress SARS-CoV-2; authorized by the FDA under EUA and Pfizer-validated), or other equivalent nucleic acid amplification–based test (i.e., NAAT) to detect SARS-CoV-2.

Planned measurements and timing of assessment

Reactogenicity and antipyretic/pain medication use was recorded for 7 days after each dose administration using an e-diary.

AEs were collected for events occurring within 1 month after each vaccination, and SAEs were collected for events occurring within 6 months after each vaccination. Acute reactions within the first 30 minutes after administration of the study intervention were recorded as immediate AEs.

AEs of myocarditis and pericarditis were collected for all participants as AESIs. Potential COVID-19 illnesses and their sequelae that were consistent with the clinical endpoint definition were not recorded as AEs or considered AESIs and were not typically reported according to the standard process for expedited reporting of SAEs.

Additionally, the MAH utilized a list of TMEs of specific clinical interest that are highlighted during clinical safety data review and signal detection. TMEs are a dynamic list of MedDRA AE terms that are reviewed on an ongoing basis throughout the clinical study; the TMEs are based on review of known pharmacology, toxicology findings, possible class effects, published literature, and potential signals arising from safety data assessments. The TME list includes events of interest due to their association

with COVID-19 and terms of interest for vaccines in general; it takes into consideration the CDC list of AESIs for COVID-19.

C4591031 Substudy D

C4591031 *Substudy D* has been designed to assess an Omicron-specific vaccine, BNT162b2 OMICRON (B.1.1.529), which is a BNT162b2 RNA-LNP vaccine utilizing modified RNA and encoding the P2 S containing Omicron variant-specific mutations (B.1.1.529 sub-variant BA.1). Interim data is presented here for participants in Cohort 2, who were enrolled from Study C4591001 and C4591031 *Substudy A* and had received 3 doses of Original 30µg, who were randomized at a ratio of 1:1 to receive a fourth dose of either BA.1 30µg or Original 30µg in C4591031 *Substudy D*. Randomization was stratified by age (18-30, 31-55 years of age). Cohort 2 was observer blinded.

Reactogenicity antipyretic/pain medication use, and collection of AEs and SAEs were evaluated similar as in *substudy E*.

5.2 Results - C4591031 Substudy E

5.2.1 Disposition and demographics

Expanded Cohort-Participants >55 years of age

Disposition of all randomized participants in the expanded cohort is summarized in Table 28 below.

Table 28. Disposition of All Randomized Participants – Expanded Cohort – Participants >55 Years of Age – Randomized Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) n[a] (%)	BNT162b2 (60 µg) n[a] (%)	BNT162b2 OMI (30 µg) n[a] (%)	BNT162b2 OMI (60 µg) n[a] (%)	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) n[a] (%)	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) n[a] (%)	Total n[a] (%)
Randomized[b]	306 (100.0)	302 (100.0)	308 (100.0)	308 (100.0)	306 (100.0)	316 (100.0)	1846 (100.0)
Not vaccinated	1 (0.3)	0	0	2 (0.6)	1 (0.3)	0	4 (0.2)
Vaccinated	305 (99.7)	302 (100.0)	308 (100.0)	306 (99.4)	305 (99.7)	316 (100.0)	1842 (99.8)
Completed 1-month post-study vaccination visit	296 (96.7)	297 (98.3)	304 (98.7)	300 (97.4)	300 (98.0)	305 (96.5)	1802 (97.6)
Withdrawn from the study	3 (1.0)	1 (0.3)	3 (1.0)	2 (0.6)	1 (0.3)	3 (0.9)	13 (0.7)
Reason for withdrawal							
No longer meets eligibility criteria	0	0	0	1 (0.3)	0	0	1 (<0.1)
Protocol deviation	0	0	1 (0.3)	1 (0.3)	0	0	2 (0.1)
Withdrawal by participant	2 (0.7)	0	0	0	1 (0.3)	2 (0.6)	5 (0.3)
Other	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)	0	1 (0.3)	6 (0.3)

a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:31) Source Data: adds Table Generation: 12JUL2022 (23:26)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File:

Disposition Sentinel Cohort-Participants >55 years of age

Table 29. Disposition of All Randomized Participants – Sentinel Cohort – Participants >55 Years of Age – Randomized Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) n[a] (%)	BNT162b2 (60 µg) n[a] (%)	BNT162b2 OMI (30 µg) n[a] (%)	BNT162b2 OMI (60 µg) n[a] (%)	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) n[a] (%)	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) n[a] (%)	Total n[a] (%)
Randomized[b]	20 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	120 (100.0)
Not vaccinated	0	0	0	0	0	0	0
Vaccinated	20 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	120 (100.0)
Completed 1-month post-study vaccination visit	20 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	120 (100.0)
Withdrawn from the study	0	0	0	0	0	0	0

a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 05MAY2022 (16:36) Source Data: adds Table Generation: 09MAY2022 (08:11)
(Data cutoff date : 05APR2022 Database snapshot date : 02MAY2022) Output File:

Safety Population-Expanded Cohort

The safety population included 1841 participants as illustrated in Table 30 below.

Table 30. Safety Population – Expanded Cohort – Participants >55 Years of Age

	Vaccine Group (as Administered)						
	BNT162b2 (30 µg) n[a]	BNT162b2 (60 µg) n[a]	BNT162b2 OMI (30 µg) n[a]	BNT162b2 OMI (60 µg) n[a]	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) n[a]	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) n[a]	Total n[a] (%)
Randomized[b]							1846
Vaccinated	305	302	307	307	305	316	1842 (99.8)
Safety population	305	302	307	306	305	316	1841 (99.7)
HIV-positive	0	2	0	3	2	2	9 (0.5)
Excluded from safety population							5 (0.3)
Reason for exclusion							
Participant did not receive study intervention							4 (0.2)
Did not provide informed consent	0	0	0	1	0	0	1 (<0.1)

Abbreviations: HIV= human immunodeficiency virus.
a. n = Number of participants with the specified characteristic, or the total sample.
b. These values are the denominators for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 27MAY2022 (12:48) Source Data: adsl Table Generation: 12JUL2022 (22:58)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File:

Follow-up time is described in Table 31 below.

Table 31. Follow-up Time After Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)						
	BNT162b2 (30 µg) (N[a]=305) n[b] (%)	BNT162b2 (60 µg) (N[a]=302) n[b] (%)	BNT162b2 OMI (30 µg) (N[a]=307) n[b] (%)	BNT162b2 OMI (60 µg) (N[a]=306) n[b] (%)	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N[a]=305) n[b] (%)	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N[a]=316) n[b] (%)	Total (N[a]=1841) n[b] (%)
Participants (%) with length of follow-up of:							
<1 Month	2 (0.7)	0	0	1 (0.3)	0	3 (0.9)	6 (0.3)
≥1 Month to <2 Months	268 (87.9)	271 (89.7)	275 (89.6)	272 (88.9)	275 (90.2)	283 (89.6)	1644 (89.3)
≥2 Months	35 (11.5)	31 (10.3)	32 (10.4)	33 (10.8)	30 (9.8)	30 (9.5)	191 (10.4)
Mean (SD)	1.7 (0.27)	1.7 (0.26)	1.7 (0.26)	1.7 (0.27)	1.7 (0.26)	1.7 (0.29)	1.7 (0.27)
Median	1.8	1.7	1.7	1.7	1.7	1.7	1.7
Min, max	(0.3, 2.0)	(1.0, 2.0)	(1.0, 2.0)	(0.6, 2.0)	(1.0, 2.0)	(0.3, 2.0)	(0.3, 2.0)

Note: Follow-up time was calculated from the first study vaccination to the cutoff date or withdrawal date, whichever date was earlier.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 27MAY2022 (12:48) Source Data: adsl Table Generation: 12JUL2022 (22:58)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File:

Safety Population-Sentinel Cohort

All 120 participants (20 participants for each group) were included in the safety population and received the vaccine.

5.2.2 Demographics

Expanded Safety Cohort- Safety

Overall, most participants in the expanded cohort safety population were White (86.6%). The median age at the time of study vaccination was 67.0 years, and 49.5% of participants were male.

Obese participants made up 35.6% of the expanded cohort. In total, 232 (12.6%) participants had baseline positive status for evidence of prior infection with SARS-CoV-2. The median time from the first booster dose of Original 30µg (received prior to the study C4591031 Substudy E) was 6.3 months.

Expanded cohort participants >55 years of age in the safety population had a diverse medical history profile consistent with the age group of this population, and medical history SOCs were generally balanced across the vaccine groups. Conditions in the SOCs of surgical and medical procedures (53.4% to 60.3%), metabolism and nutrition disorders (48.2% to 56.7%), vascular disorders (44.3% to 51.3%), musculoskeletal and connective tissue disorders (36.7% to 42.2%), and immune system disorders (32.5% to 35.8%, including 16.0% to 20.5% seasonal allergy) were most frequently reported.

Table 32. Demographic Characteristics – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)						
	BNT162b2 (30 µg) (N[a]=305) n[b] (%)	BNT162b2 (60 µg) (N[a]=302) n[b] (%)	BNT162b2 OMI (30 µg) (N[a]=307) n[b] (%)	BNT162b2 OMI (60 µg) (N[a]=306) n[b] (%)	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N[a]=305) n[b] (%)	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N[a]=316) n[b] (%)	Total (N[a]=1841) n[b] (%)
Sex							
Male	145 (47.5)	145 (48.0)	154 (50.2)	153 (50.0)	162 (53.1)	153 (48.4)	912 (49.5)
Female	160 (52.5)	157 (52.0)	153 (49.8)	153 (50.0)	143 (46.9)	163 (51.6)	929 (50.5)
Race							
White	268 (87.9)	254 (84.1)	261 (85.0)	262 (85.6)	274 (89.8)	275 (87.0)	1594 (86.6)
Black or African American	19 (6.2)	22 (7.3)	23 (7.5)	20 (6.5)	13 (4.3)	19 (6.0)	116 (6.3)
American Indian or Alaska Native	0	0	0	2 (0.7)	0	1 (0.3)	3 (0.2)
Asian	13 (4.3)	20 (6.6)	16 (5.2)	19 (6.2)	16 (5.2)	17 (5.4)	101 (5.5)
Native Hawaiian or other Pacific Islander	2 (0.7)	1 (0.3)	0	0	0	0	3 (0.2)
Multiracial	3 (1.0)	5 (1.7)	6 (2.0)	3 (1.0)	1 (0.3)	3 (0.9)	21 (1.1)
Not reported	0	0	1 (0.3)	0	1 (0.3)	1 (0.3)	3 (0.2)
Ethnicity							
Hispanic/Latino	57 (18.7)	38 (12.6)	44 (14.3)	46 (15.0)	45 (14.8)	44 (13.9)	274 (14.9)
Non-Hispanic/non-Latino	248 (81.3)	264 (87.4)	263 (85.7)	260 (85.0)	260 (85.2)	272 (86.1)	1567 (85.1)
Age at vaccination (years)							
Mean (SD)	66.4 (6.57)	67.0 (6.71)	67.0 (6.65)	66.9 (6.78)	67.4 (6.73)	67.4 (6.89)	67.0 (6.73)
Median	66.0	67.0	67.0	67.0	67.0	67.0	67.0
Min, max	(56, 87)	(56, 86)	(56, 84)	(56, 87)	(56, 85)	(56, 87)	(56, 87)

Baseline SARS-CoV-2 status							
Positive[c]	41 (13.4)	28 (9.3)	45 (14.7)	41 (13.4)	38 (12.5)	39 (12.3)	232 (12.6)
Positive NAAT	1 (0.3)	0	1 (0.3)	1 (0.3)	4 (1.3)	2 (0.6)	9 (0.5)
Negative[d]	262 (85.9)	274 (90.7)	261 (85.0)	265 (86.6)	267 (87.5)	277 (87.7)	1606 (87.2)
Missing	2 (0.7)	0	1 (0.3)	0	0	0	3 (0.2)
Time (months) from Dose 3 of BNT162b2 (received prior to the study) to the study vaccination							
n	305	302	307	306	305	316	1841
Mean (SD)	6.8 (1.44)	6.8 (1.42)	6.8 (1.37)	6.9 (1.49)	6.8 (1.39)	6.9 (1.45)	6.8 (1.43)
Median	6.3	6.3	6.3	6.3	6.3	6.3	6.3
Min, max	(5.3, 13.1)	(5.3, 12.9)	(5.1, 11.4)	(5.4, 12.8)	(4.7, 11.5)	(5.3, 11.2)	(4.7, 13.1)
<5 Months	0	0	0	0	1 (0.3)	0	1 (<0.1)
≥5 to <7 Months	234 (76.7)	235 (77.8)	233 (75.9)	223 (72.9)	230 (75.4)	229 (72.5)	1384 (75.2)
≥7 to <9 Months	40 (13.1)	39 (12.9)	47 (15.3)	48 (15.7)	43 (14.1)	51 (16.1)	268 (14.6)
≥9 to <11 Months	28 (9.2)	22 (7.3)	23 (7.5)	31 (10.1)	26 (8.5)	30 (9.5)	160 (8.7)
≥11 to <12 Months	2 (0.7)	5 (1.7)	4 (1.3)	3 (1.0)	5 (1.6)	6 (1.9)	25 (1.4)
≥12 Months	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0	3 (0.2)
Body mass index (BMI)							
Underweight (<18.5 kg/m^2)	4 (1.3)	4 (1.3)	0	3 (1.0)	1 (0.3)	3 (0.9)	15 (0.8)
Normal weight (≥18.5-24.9 kg/m^2)	85 (27.9)	91 (30.1)	79 (25.7)	78 (25.5)	71 (23.3)	84 (26.6)	488 (26.5)
Overweight (≥25.0-29.9 kg/m^2)	108 (35.4)	90 (29.8)	120 (39.1)	121 (39.5)	129 (42.3)	113 (35.8)	681 (37.0)
Obese (≥30.0 kg/m^2)	108 (35.4)	117 (38.7)	108 (35.2)	104 (34.0)	104 (34.1)	115 (36.4)	656 (35.6)
Missing	0	0	0	0	0	1 (0.3)	1 (<0.1)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
d. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
PFIZER CONFIDENTIAL SDTM Creation: 27MAY2022 (12:48) Source Data: adsl Table Generation: 12JUL2022 (23:27)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2_ube/C4591031_E_1MINEXP_EUA/adsl_s005_exp_1m_saf

E-diary Transmission

Table 33. E-Diary Transmission – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg)	BNT162b2 (60 µg)	BNT162b2 OMI (30 µg)	BNT162b2 OMI (60 µg)	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)
	n[a] (%)	n[a] (%)	n[a] (%)	n[a] (%)	n[a] (%)	n[a] (%)
Received study vaccination[b]	305	302	307	306	305	316
E-diary						
Not transmitted[c]	7 (2.3)	4 (1.3)	6 (2.0)	5 (1.6)	4 (1.3)	4 (1.3)
Transmitted[d]						
Day 1	269 (88.2)	269 (89.1)	277 (90.2)	272 (88.9)	275 (90.2)	277 (87.7)
Day 2	274 (89.8)	282 (93.4)	279 (90.9)	275 (89.9)	282 (92.5)	287 (90.8)
Day 3	277 (90.8)	271 (89.7)	274 (89.3)	269 (87.9)	274 (89.8)	285 (90.2)
Day 4	274 (89.8)	269 (89.1)	280 (91.2)	274 (89.5)	278 (91.1)	283 (89.6)
Day 5	274 (89.8)	274 (90.7)	281 (91.5)	265 (86.6)	277 (90.8)	274 (86.7)
Day 6	273 (89.5)	276 (91.4)	275 (89.6)	271 (88.6)	279 (91.5)	280 (88.6)
Day 7	266 (87.2)	277 (91.7)	276 (89.9)	269 (87.9)	269 (88.2)	281 (88.9)
All 7 days[e]	200 (65.6)	216 (71.5)	218 (71.0)	200 (65.4)	204 (66.9)	202 (63.9)

a. n = Number of participants with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. If no data for temperature, local reactions, fever/pain medication, or systemic events are reported for the entire e-diary collection period (Day 1 through Day 7), the e-diary is considered not transmitted.
d. If any data for temperature, local reactions, fever/pain medication, or systemic events are reported for the specified day or set of days (ie, "all 7 days"), the e-diary is considered transmitted.
e. "All 7 days" includes Day 1 through Day 7 after vaccination. Day 1 is the day of vaccination.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:31) Source Data: adfacevd Table Generation: 12JUL2022 (23:26)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File:

Sentinel Cohort – Safety

Table 34. Demographic Characteristics – Sentinel Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)						
	BNT162b2 (30 µg) (N[a]=20) n[b] (%)	BNT162b2 (60 µg) (N[a]=20) n[b] (%)	BNT162b2 OMI (30 µg) (N[a]=20) n[b] (%)	BNT162b2 OMI (60 µg) (N[a]=20) n[b] (%)	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N[a]=20) n[b] (%)	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N[a]=20) n[b] (%)	Total (N[a]=120) n[b] (%)
Sex							
Male	12 (60.0)	11 (55.0)	6 (30.0)	8 (40.0)	13 (65.0)	9 (45.0)	59 (49.2)
Female	8 (40.0)	9 (45.0)	14 (70.0)	12 (60.0)	7 (35.0)	11 (55.0)	61 (50.8)
Race							
White	16 (80.0)	19 (95.0)	15 (75.0)	17 (85.0)	14 (70.0)	16 (80.0)	97 (80.8)
Black or African American	1 (5.0)	0	2 (10.0)	2 (10.0)	2 (10.0)	1 (5.0)	8 (6.7)
Asian	3 (15.0)	1 (5.0)	2 (10.0)	1 (5.0)	4 (20.0)	3 (15.0)	14 (11.7)
Multiracial	0	0	1 (5.0)	0	0	0	1 (0.8)
Ethnicity							
Hispanic/Latino	1 (5.0)	1 (5.0)	4 (20.0)	3 (15.0)	2 (10.0)	4 (20.0)	15 (12.5)
Non-Hispanic/non-Latino	19 (95.0)	19 (95.0)	16 (80.0)	17 (85.0)	18 (90.0)	16 (80.0)	105 (87.5)
Age at vaccination (years)							
Mean (SD)	67.9 (7.55)	70.3 (7.77)	67.4 (5.61)	66.6 (5.55)	67.5 (5.30)	66.4 (8.04)	67.7 (6.71)
Median	68.0	71.5	66.0	66.5	67.5	67.5	67.0
Min, max	(56, 79)	(57, 84)	(56, 78)	(58, 78)	(57, 74)	(56, 85)	(56, 85)
Baseline SARS-CoV-2 status							
Positive[c]	2 (10.0)	0	3 (15.0)	2 (10.0)	4 (20.0)	1 (5.0)	12 (10.0)
Negative[d]	18 (90.0)	20 (100.0)	17 (85.0)	18 (90.0)	16 (80.0)	19 (95.0)	108 (90.0)
Time (months) from Dose 3 of BNT162b2 (received prior to the study) to the study vaccination							
n	20	20	20	20	20	20	120
Mean (SD)	8.4 (0.93)	8.7 (1.05)	8.1 (0.75)	8.4 (0.97)	8.6 (0.98)	8.6 (0.93)	8.5 (0.94)
Median	7.9	8.1	7.9	8.0	8.1	8.1	8.0
Min, max	(7.3, 10.0)	(7.4, 10.0)	(7.4, 9.9)	(7.3, 10.0)	(7.4, 10.0)	(7.3, 10.0)	(7.3, 10.0)
≥7 to <9 Months	14 (70.0)	12 (60.0)	17 (85.0)	14 (70.0)	13 (65.0)	13 (65.0)	83 (69.2)
≥9 to <11 Months	6 (30.0)	8 (40.0)	3 (15.0)	6 (30.0)	7 (35.0)	7 (35.0)	37 (30.8)
Body mass index (BMI)							
Underweight (<18.5 kg/m^2)	0	0	1 (5.0)	0	0	0	1 (0.8)
Normal weight (≥18.5-24.9 kg/m^2)	5 (25.0)	4 (20.0)	4 (20.0)	5 (25.0)	6 (30.0)	6 (30.0)	30 (25.0)
Overweight (≥25.0-29.9 kg/m^2)	6 (30.0)	8 (40.0)	8 (40.0)	9 (45.0)	6 (30.0)	8 (40.0)	45 (37.5)
Obese (≥30.0 kg/m^2)	9 (45.0)	8 (40.0)	7 (35.0)	6 (30.0)	8 (40.0)	6 (30.0)	44 (36.7)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
d. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
PFIZER CONFIDENTIAL SDTM Creation: 05MAY2022 (16:36) Source Data: adsl Table Generation: 06MAY2022 (23:48)
(Data cutoff date : 05APR2022 Database snapshot date : 02MAY2022) Output File: /ada3/C4591031_E_IMSentinel/adsl_s005_sen_1ns_saf

In the sentinel cohort, transmission of e-diary data for each day during the 7 days after study vaccination ranged from 85.0% to 100.0%.

5.2.3 Reactogenicity

Expanded Cohort

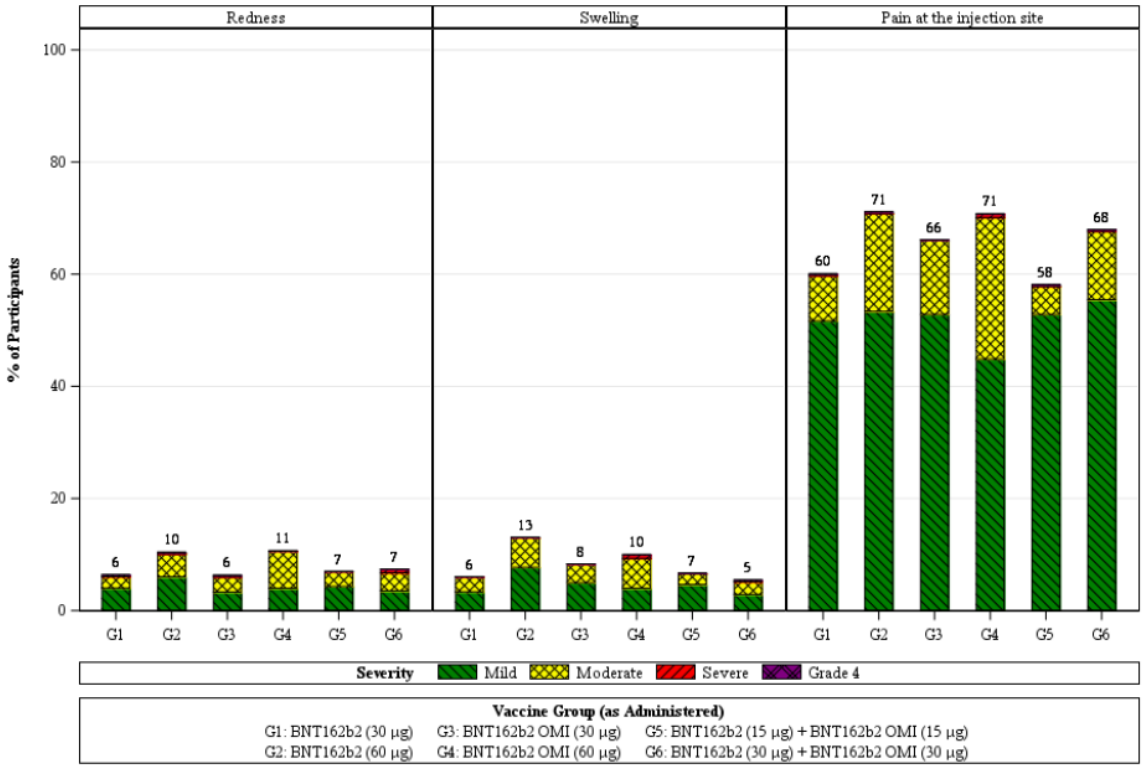
Local reactions

Pain at injection site was the most frequently reported local reaction within 7 days after study vaccination, with swelling and redness at the injection site reported much less frequently. Frequency of injection site pain was slightly higher for participants in the following groups Original 60µg, BA.1 60µg, and Original/BA.1 30/30µg.

Most local reactions were mild or moderate in severity. Severe local reactions were reported infrequently in all vaccine groups; severe events after study vaccination included injection site pain (0.3%), swelling (0.2%) and redness (0.3%). No Grade 4 local reactions were reported in any vaccine groups evaluated.

The median onset for all local reactions across vaccine groups evaluated was 2 days, and all events resolved within a median duration of 1 to 2 days after onset.

Figure 5. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population



Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:31) Source Data: adfacevd Table Generation: 12JUL2022 (23:26)
(Data Cutoff Date: 16MAY2022, Database Snapshot Date: 26MAY2022) Output File: /nda2_ube/C4591031_E_1MINEXP_EUA/adce_f001_exp_lr_1m

Severity of local reactions

Table 35. Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)											
	BNT162b2 (30 µg)		BNT162b2 (60 µg)		BNT162b2 OMI (30 µg)		BNT162b2 OMI (60 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)	
Local Reaction	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])
Redness[d]												
Any	298	19 (6.4) (3.9, 9.8)	298	31 (10.4) (7.2, 14.4)	301	19 (6.3) (3.8, 9.7)	301	32 (10.6) (7.4, 14.7)	301	21 (7.0) (4.4, 10.5)	312	23 (7.4) (4.7, 10.9)
Mild	298	12 (4.0) (2.1, 6.9)	298	18 (6.0) (3.6, 9.4)	301	10 (3.3) (1.6, 6.0)	301	12 (4.0) (2.1, 6.9)	301	13 (4.3) (2.3, 7.3)	312	11 (3.5) (1.8, 6.2)
Moderate	298	6 (2.0) (0.7, 4.3)	298	12 (4.0) (2.1, 6.9)	301	8 (2.7) (1.2, 5.2)	301	20 (6.6) (4.1, 10.1)	301	8 (2.7) (1.2, 5.2)	312	10 (3.2) (1.5, 5.8)
Severe	298	1 (0.3) (0.0, 1.9)	298	1 (0.3) (0.0, 1.9)	301	1 (0.3) (0.0, 1.8)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	2 (0.6) (0.1, 2.3)
Grade 4	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
Swelling[d]												
Any	298	18 (6.0) (3.6, 9.4)	298	39 (13.1) (9.5, 17.5)	301	25 (8.3) (5.4, 12.0)	301	30 (10.0) (6.8, 13.9)	301	20 (6.6) (4.1, 10.1)	312	17 (5.4) (3.2, 8.6)
Mild	298	10 (3.4) (1.6, 6.1)	298	23 (7.7) (5.0, 11.4)	301	15 (5.0) (2.8, 8.1)	301	12 (4.0) (2.1, 6.9)	301	14 (4.7) (2.6, 7.7)	312	9 (2.9) (1.3, 5.4)
Moderate	298	8 (2.7) (1.2, 5.2)	298	16 (5.4) (3.1, 8.6)	301	10 (3.3) (1.6, 6.0)	301	16 (5.3) (3.1, 8.5)	301	6 (2.0) (0.7, 4.3)	312	7 (2.2) (0.9, 4.6)
Severe	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	2 (0.7) (0.1, 2.4)	301	0 (0.0, 1.2)	312	1 (0.3) (0.0, 1.8)
Grade 4	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
Pain at the injection site[e]												
Any	298	179 (60.1) (54.3, 65.7)	298	212 (71.1) (65.6, 76.2)	301	199 (66.1) (60.5, 71.4)	301	213 (70.8) (65.3, 75.8)	301	175 (58.1) (52.3, 63.8)	312	212 (67.9) (62.5, 73.1)
Mild	298	154 (51.7) (45.8, 57.5)	298	159 (53.4) (47.5, 59.1)	301	159 (52.8) (47.0, 58.6)	301	135 (44.9) (39.1, 50.7)	301	159 (52.8) (47.0, 58.6)	312	173 (55.4) (49.7, 61.0)
Moderate	298	24 (8.1) (5.2, 11.7)	298	52 (17.4) (13.3, 22.2)	301	40 (13.3) (9.7, 17.7)	301	76 (25.2) (20.4, 30.6)	301	15 (5.0) (2.8, 8.1)	312	38 (12.2) (8.8, 16.3)
Severe	298	1 (0.3) (0.0, 1.9)	298	1 (0.3) (0.0, 1.9)	301	0 (0.0, 1.2)	301	2 (0.7) (0.1, 2.4)	301	1 (0.3) (0.0, 1.8)	312	1 (0.3) (0.0, 1.8)

Grade 4	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
Any local reaction[f]	298	182 (61.1) (55.3, 66.6)	298	214 (71.8) (66.3, 76.8)	301	205 (68.1) (62.5, 73.3)	301	217 (72.1) (66.7, 77.1)	301	179 (59.5) (53.7, 65.1)	312	216 (69.2) (63.8, 74.3)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 through Day 7 after the study vaccination.
Note: Grade 4 reactions were classified by the investigator or medically qualified person.
a. N = number of participants reporting at least 1 yes or no response for the specified reaction after the study vaccination.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
d. Mild: >2.0 to 5.0 cm; moderate: >5.0 to 10.0 cm; severe: >10.0 cm; Grade 4: necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).
e. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe pain at the injection site.
f. Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:31) Source Data: adfacevd Table Generation: 12JUL2022 (23:26)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File:

Time to onset

Table 36. Onset Days for Local Reactions After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)					
Local Reaction	**BNT162b2 (30 µg)**	**BNT162b2 (60 µg)**	**BNT162b2 OMI (30 µg)**	**BNT162b2 OMI (60 µg)**	**BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)**	**BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)**
Redness						
n[a]	19	31	19	32	21	23
Mean (SD)	2.3 (0.58)	2.6 (0.99)	2.5 (0.84)	2.7 (0.94)	2.2 (1.00)	2.5 (0.90)
Median	2.0	2.0	2.0	3.0	2.0	2.0
Min, max	(1, 3)	(1, 6)	(1, 4)	(1, 5)	(1, 5)	(1, 5)
Swelling						
n[a]	18	39	25	30	20	17
Mean (SD)	2.1 (0.54)	1.8 (0.59)	2.1 (0.57)	2.3 (0.99)	2.3 (0.91)	2.0 (0.71)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 3)	(1, 4)	(1, 3)	(1, 6)	(1, 5)	(1, 3)
Pain at the injection site						
n[a]	179	212	199	213	175	212
Mean (SD)	1.6 (0.55)	1.6 (0.64)	1.7 (0.64)	1.6 (0.61)	1.7 (0.71)	1.6 (0.59)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 3)	(1, 6)	(1, 5)	(1, 6)	(1, 6)	(1, 4)
Any local reaction[b]						
n[a]	182	214	205	217	179	216
Mean (SD)	1.6 (0.57)	1.6 (0.69)	1.7 (0.67)	1.6 (0.62)	1.7 (0.71)	1.7 (0.61)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 3)	(1, 6)	(1, 5)	(1, 6)	(1, 6)	(1, 4)

Note: Day of onset is the first day the specified reaction was reported.
a. n = Number of participants reporting the specified reaction, with each participant counted only once per reaction.
b. Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:31) Source Data: adfacevd Table Generation: 12JUL2022 (23:26)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: /nda2_ube/C4591031_E_1MINEXP_EUA/adce_s050_exp_lr_onset_1m

Duration of local reactions

Table 37. Duration (Days) From First to Last Day of Local Reactions – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)					
Local Reaction	**BNT162b2 (30 µg)**	**BNT162b2 (60 µg)**	**BNT162b2 OMI (30 µg)**	**BNT162b2 OMI (60 µg)**	**BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)**	**BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)**
Redness						
n[a]	19	31	19	32	21	23
Mean (SD)	1.9 (1.33)	1.9 (1.41)	2.7 (2.70)	2.4 (1.95)	2.9 (2.61)	2.4 (1.62)
Median	1.0	1.0	2.0	2.0	2.0	2.0
Min, max	(1, 5)	(1, 7)	(1, 12)	(1, 9)	(1, 10)	(1, 8)
Swelling						
n[a]	18	39	25	30	20	17
Mean (SD)	1.8 (1.15)	1.8 (1.16)	2.8 (2.26)	2.7 (1.71)	1.9 (1.17)	2.5 (1.59)
Median	1.0	1.0	2.0	2.0	1.5	2.0
Min, max	(1, 4)	(1, 5)	(1, 10)	(1, 8)	(1, 4)	(1, 7)
Pain at the injection site						
n[a]	179	212	199	213	175	212
Mean (SD)	2.2 (1.41)	2.6 (3.16)	2.5 (2.30)	2.5 (1.63)	2.2 (1.72)	2.2 (1.29)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 7)	(1, 43)	(1, 25)	(1, 12)	(1, 12)	(1, 9)
Unknown[b]	0	1	0	0	0	0

Note: Duration was calculated in days as the difference from the start of the first reported reaction to the resolution of the last reported reaction, inclusive.
Note: Reactions were recorded in the electronic diary (e-diary) from Day 1 through Day 7 after the study vaccination. The resolution date for reactions ongoing on the last day of e-diary completion was recorded on the participant's case report form.
a. n = Number of participants reporting the specified reaction on any of the 7 days, including participants with reactions of unknown duration.
b. Includes those reactions where the resolution date is partial or missing.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:30) Source Data: adcevd Table Generation: 12JUL2022 (23:27)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: /nda2_ube/C4591031_E_1MINEXP_EUA/adce_s030_exp_lr_dur_1m

Subgroup Analyses

While there were numerical differences between subgroups, no clinically meaningful patterns within or between groups were noted with regard to local reactions, across all vaccine groups when evaluated by subgroups of race, ethnicity and baseline SARS-CoV-2 status. These subgroups included a limited number of participants, and their results should be interpreted with caution.

Sex

The frequencies of local reactions reported after study vaccination in the sex subgroups of participants >55 years of age were:

		BNT162b2		BNT162b2 OMI		BNT162b2 + BNT162b2 OMI	
		30 µg	**60 µg**	**30 µg**	**60 µg**	**30 µg**	**60 µg**
	Male	n=140	n=142	n=148	n=151	n=158	n=149
	Female	n=158	n=156	n=153	n=150	n=143	n=163
Pain at injection site							
	Male	50.0%	66.9%	56.8%	64.9%	52.5%	56.4%
	Female	69.0%	75.0%	75.2%	76.7%	64.3%	78.5%
Redness							
	Male	1.4%	5.6%	4.1%	7.3%	3.8%,	3.4%
	Female	10.8%	14.7%	8.5%	14.0%	10.5%	11.0%
Swelling							
	Male	2.1%	7.7%	5.4%	7.3%	6.3%	2.7%
	Female	9.5%	17.9%	11.1%	12.7%	7.0%	8.0%

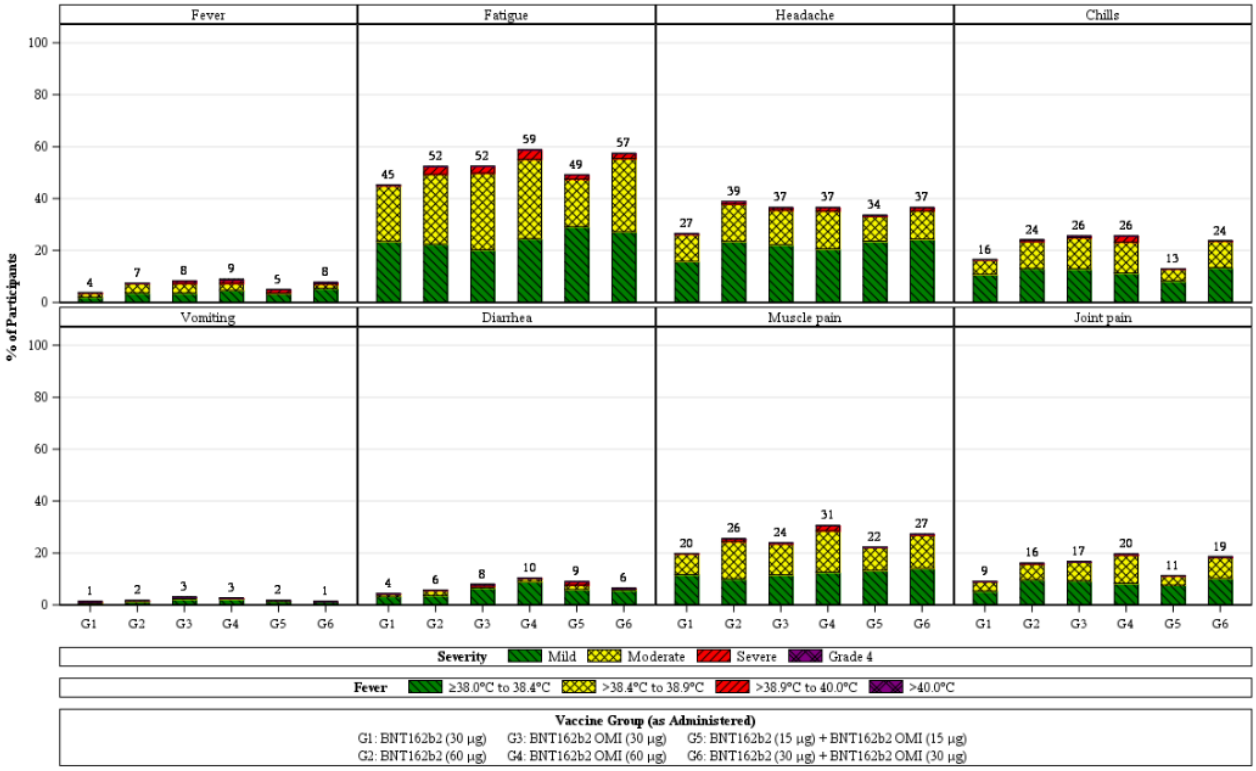
Systemic reactions

Fatigue was the most frequently reported systemic event, followed by headache, and less frequently chills, muscle and joint pain (Figure 6). In general, systemic events were reported at slightly higher frequencies for participants in the 60-µg dose groups.

Most systemic events were mild or moderate in severity. Severe events were relatively more frequent in the BA.1 60µg group.

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

Figure 6. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population



Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:31) Source Data: adfacevd Table Generation: 12JUL2022 (23:26)
(Data Cutoff Date: 16MAY2022, Database Snapshot Date: 26MAY2022) Output File: /nda2_ube/C4591031_E_1MINEXP_EUA/adce_f001_exp_se_1m

Severity of systemic reactions

Table 38. Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)											
	BNT162b2 (30 µg)		BNT162b2 (60 µg)		BNT162b2 OMI (30 µg)		BNT162b2 OMI (60 µg)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)	
Systemic Event	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])
Fever												
≥38.0°C	298	11 (3.7) (1.9, 6.5)	298	22 (7.4) (4.7, 11.0)	301	25 (8.3) (5.4, 12.0)	301	27 (9.0) (6.0, 12.8)	301	15 (5.0) (2.8, 8.1)	312	24 (7.7) (5.0, 11.2)
≥38.0°C to 38.4°C	298	6 (2.0) (0.7, 4.3)	298	11 (3.7) (1.9, 6.5)	301	11 (3.7) (1.8, 6.4)	301	14 (4.7) (2.6, 7.7)	301	11 (3.7) (1.8, 6.4)	312	17 (5.4) (3.2, 8.6)
>38.4°C to 38.9°C	298	5 (1.7) (0.5, 3.9)	298	11 (3.7) (1.9, 6.5)	301	11 (3.7) (1.8, 6.4)	301	8 (2.7) (1.2, 5.2)	301	0 (0.0, 1.2)	312	5 (1.6) (0.5, 3.7)
>38.9°C to 40.0°C	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	3 (1.0) (0.2, 2.9)	301	4 (1.3) (0.4, 3.4)	301	4 (1.3) (0.4, 3.4)	312	2 (0.6) (0.1, 2.3)
>40.0°C	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	1 (0.3) (0.0, 1.8)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
Fatigue[d]												
Any	298	135 (45.3) (39.6, 51.1)	298	156 (52.3) (46.5, 58.1)	301	158 (52.5) (46.7, 58.3)	301	177 (58.8) (53.0, 64.4)	301	148 (49.2) (43.4, 55.0)	312	179 (57.4) (51.7, 62.9)
Mild	298	70 (23.5) (18.8, 28.7)	298	67 (22.5) (17.9, 27.7)	301	61 (20.3) (15.9, 25.3)	301	74 (24.6) (19.8, 29.9)	301	88 (29.2) (24.2, 34.7)	312	85 (27.2) (22.4, 32.5)
Moderate	298	64 (21.5) (17.0, 26.6)	298	80 (26.8) (21.9, 32.3)	301	89 (29.6) (24.5, 35.1)	301	92 (30.6) (25.4, 36.1)	301	55 (18.3) (14.1, 23.1)	312	88 (28.2) (23.3, 33.5)
Severe	298	1 (0.3) (0.0, 1.9)	298	9 (3.0) (1.4, 5.7)	301	8 (2.7) (1.2, 5.2)	301	11 (3.7) (1.8, 6.4)	301	5 (1.7) (0.5, 3.8)	312	6 (1.9) (0.7, 4.1)
Grade 4	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
Headache[d]												
Any	298	79 (26.5) (21.6, 31.9)	298	116 (38.9) (33.4, 44.7)	301	110 (36.5) (31.1, 42.3)	301	110 (36.5) (31.1, 42.3)	301	101 (33.6) (28.2, 39.2)	312	114 (36.5) (31.2, 42.1)
Mild	298	47 (15.8) (11.8, 20.4)	298	70 (23.5) (18.8, 28.7)	301	67 (22.3) (17.7, 27.4)	301	62 (20.6) (16.2, 25.6)	301	71 (23.6) (18.9, 28.8)	312	76 (24.4) (19.7, 29.5)

Moderate	298	31 (10.4) (7.2, 14.4)	298	43 (14.4) (10.6, 18.9)	301	40 (13.3) (9.7, 17.7)	301	44 (14.6) (10.8, 19.1)	301	29 (9.6) (6.5, 13.5)	312	34 (10.9) (7.7, 14.9)
Severe	298	1 (0.3) (0.0, 1.9)	298	3 (1.0) (0.2, 2.9)	301	3 (1.0) (0.2, 2.9)	301	4 (1.3) (0.4, 3.4)	301	1 (0.3) (0.0, 1.8)	312	4 (1.3) (0.4, 3.2)
Grade 4	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
Chills[d]												
Any	298	49 (16.4) (12.4, 21.1)	298	72 (24.2) (19.4, 29.4)	301	77 (25.6) (20.7, 30.9)	301	77 (25.6) (20.7, 30.9)	301	39 (13.0) (9.4, 17.3)	312	74 (23.7) (19.1, 28.8)
Mild	298	32 (10.7) (7.5, 14.8)	298	39 (13.1) (9.5, 17.5)	301	39 (13.0) (9.4, 17.3)	301	34 (11.3) (8.0, 15.4)	301	25 (8.3) (5.4, 12.0)	312	42 (13.5) (9.9, 17.8)
Moderate	298	17 (5.7) (3.4, 9.0)	298	31 (10.4) (7.2, 14.4)	301	36 (12.0) (8.5, 16.2)	301	36 (12.0) (8.5, 16.2)	301	14 (4.7) (2.6, 7.7)	312	32 (10.3) (7.1, 14.2)
Severe	298	0 (0.0, 1.2)	298	2 (0.7) (0.1, 2.4)	301	2 (0.7) (0.1, 2.4)	301	7 (2.3) (0.9, 4.7)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
Grade 4	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
Vomiting[e]												
Any	298	4 (1.3) (0.4, 3.4)	298	5 (1.7) (0.5, 3.9)	301	9 (3.0) (1.4, 5.6)	301	8 (2.7) (1.2, 5.2)	301	5 (1.7) (0.5, 3.8)	312	4 (1.3) (0.4, 3.2)
Mild	298	2 (0.7) (0.1, 2.4)	298	4 (1.3) (0.4, 3.4)	301	7 (2.3) (0.9, 4.7)	301	7 (2.3) (0.9, 4.7)	301	5 (1.7) (0.5, 3.8)	312	4 (1.3) (0.4, 3.2)
Moderate	298	2 (0.7) (0.1, 2.4)	298	1 (0.3) (0.0, 1.9)	301	2 (0.7) (0.1, 2.4)	301	1 (0.3) (0.0, 1.8)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
Severe	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
Grade 4	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
Diarrhea[f]												
Any	298	13 (4.4) (2.3, 7.3)	298	17 (5.7) (3.4, 9.0)	301	24 (8.0) (5.2, 11.6)	301	31 (10.3) (7.1, 14.3)	301	27 (9.0) (6.0, 12.8)	312	20 (6.4) (4.0, 9.7)

Mild	298	10 (3.4) (1.6, 6.1)	298	11 (3.7) (1.9, 6.5)	301	20 (6.6) (4.1, 10.1)	301	27 (9.0) (6.0, 12.8)	301	18 (6.0) (3.6, 9.3)	312	18 (5.8) (3.5, 9.0)
Moderate	298	3 (1.0) (0.2, 2.9)	298	6 (2.0) (0.7, 4.3)	301	2 (0.7) (0.1, 2.4)	301	4 (1.3) (0.4, 3.4)	301	5 (1.7) (0.5, 3.8)	312	2 (0.6) (0.1, 2.3)
Severe	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	2 (0.7) (0.1, 2.4)	301	0 (0.0, 1.2)	301	4 (1.3) (0.4, 3.4)	312	0 (0.0, 1.2)
Grade 4	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
New or worsened muscle pain[d]												
Any	298	59 (19.8) (15.4, 24.8)	298	76 (25.5) (20.7, 30.8)	301	72 (23.9) (19.2, 29.1)	301	92 (30.6) (25.4, 36.1)	301	67 (22.3) (17.7, 27.4)	312	85 (27.2) (22.4, 32.5)
Mild	298	35 (11.7) (8.3, 16.0)	298	30 (10.1) (6.9, 14.1)	301	35 (11.6) (8.2, 15.8)	301	38 (12.6) (9.1, 16.9)	301	40 (13.3) (9.7, 17.7)	312	44 (14.1) (10.4, 18.5)
Moderate	298	24 (8.1) (5.2, 11.7)	298	43 (14.4) (10.6, 18.9)	301	36 (12.0) (8.5, 16.2)	301	48 (15.9) (12.0, 20.6)	301	27 (9.0) (6.0, 12.8)	312	40 (12.8) (9.3, 17.0)
Severe	298	0 (0.0, 1.2)	298	3 (1.0) (0.2, 2.9)	301	1 (0.3) (0.0, 1.8)	301	6 (2.0) (0.7, 4.3)	301	0 (0.0, 1.2)	312	1 (0.3) (0.0, 1.8)
Grade 4	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)
New or worsened joint pain[d]												
Any	298	27 (9.1) (6.1, 12.9)	298	48 (16.1) (12.1, 20.8)	301	50 (16.6) (12.6, 21.3)	301	59 (19.6) (15.3, 24.5)	301	34 (11.3) (8.0, 15.4)	312	58 (18.6) (14.4, 23.4)
Mild	298	16 (5.4) (3.1, 8.6)	298	29 (9.7) (6.6, 13.7)	301	28 (9.3) (6.3, 13.2)	301	25 (8.3) (5.4, 12.0)	301	23 (7.6) (4.9, 11.2)	312	32 (10.3) (7.1, 14.2)
Moderate	298	11 (3.7) (1.9, 6.5)	298	18 (6.0) (3.6, 9.4)	301	22 (7.3) (4.6, 10.9)	301	33 (11.0) (7.7, 15.1)	301	11 (3.7) (1.8, 6.4)	312	25 (8.0) (5.3, 11.6)
Severe	298	0 (0.0, 1.2)	298	1 (0.3) (0.0, 1.9)	301	0 (0.0, 1.2)	301	1 (0.3) (0.0, 1.8)	301	0 (0.0, 1.2)	312	1 (0.3) (0.0, 1.8)
Grade 4	298	0 (0.0, 1.2)	298	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	301	0 (0.0, 1.2)	312	0 (0.0, 1.2)

Any systemic event[g]	298	167 (56.0) (50.2, 61.8)	298	195 (65.4) (59.7, 70.8)	301	192 (63.8) (58.1, 69.2)	301	204 (67.8) (62.2, 73.0)	301	182 (60.5) (54.7, 66.0)	312	211 (67.6) (62.1, 72.8)
Use of antipyretic or pain medication[h]	298	80 (26.8) (21.9, 32.3)	298	111 (37.2) (31.7, 43.0)	301	105 (34.9) (29.5, 40.6)	301	109 (36.2) (30.8, 41.9)	301	88 (29.2) (24.2, 34.7)	312	108 (34.6) (29.3, 40.2)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 through Day 7 after the study vaccination.
Note: Grade 4 events were classified by the investigator or medically qualified person.
a. N = number of participants reporting at least 1 yes or no response for the specified event after the study vaccination.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
d. Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe fatigue, severe headache, severe chills, severe muscle pain, or severe joint pain.
e. Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration; Grade 4: emergency room visit or hospitalization for severe vomiting.
f. Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours; Grade 4: emergency room visit or hospitalization for severe diarrhea.
g. Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
h. Severity was not collected for use of antipyretic or pain medication.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:31) Source Data: adfacevd Table Generation: 12JUL2022 (23:27)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2_ube/C4591031_E_1MINEXP_EUA/adce_s020_exp_se_1m

Time to onset of systemic reactions

Table 39. Onset Days for Systemic Events After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)					
Systemic Event	**BNT162b2 (30 µg)**	**BNT162b2 (60 µg)**	**BNT162b2 OMI (30 µg)**	**BNT162b2 OMI (60 µg)**	**BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)**	**BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)**
Fever (≥38.0°C)						
n[a]	11	22	25	27	15	24
Mean (SD)	2.3 (0.90)	2.1 (0.92)	2.1 (1.05)	2.0 (0.34)	2.2 (0.77)	2.1 (0.65)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(2, 5)	(1, 6)	(1, 7)	(1, 3)	(2, 5)	(1, 5)
Fatigue						
n[a]	135	156	158	177	148	179
Mean (SD)	1.9 (0.69)	1.9 (0.98)	1.9 (0.92)	2.0 (0.95)	2.0 (1.03)	1.9 (0.63)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 4)	(1, 7)	(1, 7)	(1, 7)	(1, 7)	(1, 4)
Headache						
n[a]	79	116	110	110	101	114
Mean (SD)	2.3 (1.24)	2.0 (0.91)	2.2 (1.20)	2.2 (1.30)	2.4 (1.37)	2.3 (1.21)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 7)	(1, 7)	(1, 7)	(1, 7)	(1, 7)	(1, 7)
Chills						
n[a]	49	72	77	77	39	74
Mean (SD)	2.0 (0.48)	2.0 (0.88)	2.3 (1.17)	2.2 (1.04)	2.2 (1.20)	2.1 (0.92)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 4)	(1, 5)	(1, 7)	(1, 7)	(1, 7)	(1, 6)
Vomiting						
n[a]	4	5	9	8	5	4
Mean (SD)	3.0 (2.00)	3.0 (2.24)	3.4 (2.13)	2.8 (1.16)	3.6 (0.89)	3.5 (2.38)
Median	2.0	2.0	2.0	2.0	3.0	2.5
Min, max	(2, 6)	(2, 7)	(1, 7)	(2, 5)	(3, 5)	(2, 7)
Diarrhea						
n[a]	13	17	24	31	27	20
Mean (SD)	2.7 (1.75)	3.2 (1.89)	3.4 (1.69)	3.4 (1.89)	3.5 (1.97)	3.1 (1.37)
Median	2.0	3.0	3.0	3.0	3.0	3.0
Min, max	(1, 6)	(1, 7)	(1, 7)	(1, 7)	(1, 7)	(1, 7)
New or worsened muscle pain						
n[a]	59	76	72	92	67	85
Mean (SD)	2.4 (1.23)	2.3 (1.28)	2.3 (1.05)	2.1 (0.97)	2.4 (1.35)	2.1 (0.52)

Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 7)	(1, 7)	(1, 7)	(1, 6)	(1, 7)	(1, 4)
New or worsened joint pain						
n[a]	27	48	50	59	34	58
Mean (SD)	2.4 (1.15)	2.4 (1.25)	2.4 (1.14)	2.2 (0.95)	2.9 (1.67)	2.2 (0.81)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(2, 7)	(1, 7)	(1, 7)	(1, 6)	(1, 7)	(1, 6)
Any systemic event[b]						
n[a]	167	195	192	204	182	211
Mean (SD)	1.9 (0.89)	1.9 (1.07)	1.9 (0.92)	2.0 (1.16)	2.0 (1.13)	1.9 (0.75)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 7)	(1, 7)	(1, 7)	(1, 7)	(1, 7)	(1, 6)
Use of antipyretic or pain medication						
n[a]	80	111	105	109	88	108
Mean (SD)	2.6 (1.50)	2.1 (1.08)	2.3 (1.27)	2.1 (1.02)	2.2 (1.26)	2.0 (0.59)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 7)	(1, 7)	(1, 7)	(1, 6)	(1, 7)	(1, 5)

Note: Day of onset is the first day the specified event was reported.
a. n = Number of participants reporting the specified event, with each participant counted only once per event.
b. Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:31) Source Data: adfacevd Table Generation: 12JUL2022 (23:26)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File:

Duration of systemic events

Table 40. Duration (Days) From First to Last Day of Systemic Events – Expanded Cohort – Participants >55 Years of Age – Safety Population

Systemic Event	Vaccine Group (as Administered)					
	BNT162b2 (30 µg)	BNT162b2 (60 µg)	BNT162b2 OMI (30 µg)	BNT162b2 OMI (60 µg)	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg)	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg)
Fever (≥38.0°C)						
n[a]	11	22	25	27	15	24
Mean (SD)	1.0 (0.00)	1.1 (0.47)	1.1 (0.28)	1.1 (0.27)	1.1 (0.26)	1.0 (0.00)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 1)	(1, 3)	(1, 2)	(1, 2)	(1, 2)	(1, 1)
Fatigue						
n[a]	135	156	158	177	148	179
Mean (SD)	2.1 (2.02)	2.6 (3.34)	2.6 (2.28)	2.6 (2.74)	2.7 (3.62)	2.3 (2.29)
Median	1.0	1.0	2.0	2.0	2.0	1.0
Min, max	(1, 13)	(1, 34)	(1, 13)	(1, 25)	(1, 35)	(1, 13)
Unknown[b]	0	0	0	1	0	0
Headache						
n[a]	79	116	110	110	101	114
Mean (SD)	1.9 (1.62)	2.1 (1.86)	2.2 (2.27)	2.0 (1.80)	2.4 (3.91)	2.1 (1.79)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 8)	(1, 8)	(1, 16)	(1, 10)	(1, 35)	(1, 9)
Chills						
n[a]	49	72	77	77	39	74
Mean (SD)	1.2 (0.51)	1.5 (1.01)	1.3 (0.86)	1.3 (0.78)	1.7 (2.36)	1.2 (0.79)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 4)	(1, 7)	(1, 6)	(1, 6)	(1, 15)	(1, 7)
Vomiting						
n[a]	4	5	9	8	5	4
Mean (SD)	1.0 (0.00)	1.0 (0.00)	1.1 (0.33)	1.3 (0.71)	1.2 (0.45)	1.3 (0.50)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 1)	(1, 1)	(1, 2)	(1, 3)	(1, 2)	(1, 2)
Diarrhea						
n[a]	13	17	24	31	27	20
Mean (SD)	1.0 (0.00)	2.2 (1.63)	2.5 (4.06)	1.4 (0.99)	1.7 (1.35)	1.7 (1.18)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 1)	(1, 6)	(1, 20)	(1, 5)	(1, 6)	(1, 5)
New or worsened muscle pain						
n[a]	59	76	72	92	67	85

Mean (SD)	1.5 (1.18)	1.9 (3.58)	1.3 (1.05)	1.5 (1.42)	2.4 (5.43)	1.4 (1.07)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 7)	(1, 30)	(1, 7)	(1, 11)	(1, 44)	(1, 9)
New or worsened joint pain						
n[a]	27	48	50	59	34	58
Mean (SD)	1.3 (0.78)	1.6 (1.63)	1.4 (1.11)	1.4 (1.07)	2.7 (7.40)	1.3 (0.61)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 4)	(1, 11)	(1, 6)	(1, 6)	(1, 44)	(1, 4)
Unknown[b]	0	0	0	0	0	1
Use of antipyretic or pain medication						
n[a]	80	111	105	109	88	108
Mean (SD)	1.8 (1.49)	1.7 (1.37)	2.1 (1.85)	1.9 (1.63)	2.8 (4.38)	1.9 (2.21)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 7)	(1, 8)	(1, 9)	(1, 9)	(1, 35)	(1, 19)
Unknown[b]	0	0	0	0	0	1

Note: Duration was calculated in days as the difference from the start of the first reported event to the resolution of the last reported event, inclusive.
Note: Events and use of antipyretic or pain medication were recorded in the electronic diary (e-diary) from Day 1 through Day 7 after the study vaccination. The resolution date for events ongoing on the last day of e-diary completion was recorded on the participant's case report form.
a. n = Number of participants reporting the specified event on any of the 7 days, including participants with events of unknown duration.
b. Includes those events where the resolution date is partial or missing.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:30) Source Data: adcevd Table Generation: 12JUL2022 (23:27)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File:

Subgroup Analyses

While there were numerical differences between subgroups, no clinically meaningful patterns within or between groups were noted with regard to systemic events, across all vaccine groups when evaluated by subgroups of race, ethnicity and baseline SARS-CoV-2 status. These subgroups included a limited number of participants, and their results should be interpreted with caution.

Sex

The frequencies of systemic events reported after study vaccination in the sex subgroups of participants >55 years of age were:

		BNT162b2		BNT162b2 OMI		BNT162b2 + BNT162b2 OMI	
		30 µg	60 µg	30 µg	60 µg	30 µg	60 µg
	Male	n=140	n=142	n=148	n=151	n=158	n=149
	Female	n=158	n=156	n=153	n=150	n=143	n=163
Fatigue	Male	34.3%	47.9%	41.2%	55.0%	41.8%	47.7%
	Female	55.1%	56.4%	63.4%	62.7%	57.3%	66.3%
Headache	Male	20.7%	35.2%	23.0%	28.5%	27.2%	26.8%
	Female	31.6%	42.3%	49.7%	44.7%	40.6%	45.4%
Muscle pain	Male	17.9%	24.6%	20.9%	27.2%	18.4%	22.1%
	Female	21.5%	26.3%	26.8%	34.0%	26.6%	31.9%
Chills	Male	13.6%	21.8%	20.3%	21.9%	10.8%	17.4%
	Female	19.0%	26.3%	30.7%	29.3%	15.4%	29.4%
Joint pain	Male	6.4%	15.5%	12.8%	15.9%	8.2%	13.4%
	Female	11.4%	16.7%	20.3%	23.3%	14.7%	23.3%
Fever	Male	1.4%	7.7%	8.8%	5.3%	3.8%	8.1%
	Female	5.7%	7.1%	7.8%	12.7%	6.3%	7.4%

5.2.4 Adverse events

Adverse events – expanded cohort

Adverse Events from Study Vaccination to Data Cutoff Date

An overview of AEs from study vaccination to data cutoff date (16 May 2022), which represents a median follow-up of at least 1.7 months after study vaccination, is presented in Table 20.

From study vaccination to the data cutoff date, the proportions of participants with any AEs were generally similar. In addition to events already reported up to 1-month post- Dose (Table 19, see below), a limited number of additional events were reported up to the data cutoff date. As of the data cutoff date, any related or any severe AEs were reported across the vaccine groups by ≤5.1% or ≤0.9% of participants, respectively. Two additional severe AEs, also reported as SAEs (pneumonia, ischaemic stroke) were reported in the Original 30µg group (see, adverse Events from study vaccination to data cutoff date). No withdrawals due to AEs were reported in any of the groups beyond 1-month post-Dose. No study participants died.

Table 41. Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through Cutoff Date – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N[a]=305)	BNT162b2 (60 µg) (N[a]=302)	BNT162b2 OMI (30 µg) (N[a]=307)	BNT162b2 OMI (60 µg) (N[a]=306)	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N[a]=305)	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N[a]=316)
Adverse Event	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any adverse event	20 (6.6)	23 (7.6)	26 (8.5)	12 (3.9)	19 (6.2)	33 (10.4)
Related[c]	4 (1.3)	13 (4.3)	10 (3.3)	5 (1.6)	7 (2.3)	16 (5.1)
Severe	2 (0.7)	0	1 (0.3)	0	1 (0.3)	3 (0.9)
Life-threatening	0	0	0	0	0	1 (0.3)
Any serious adverse event	2 (0.7)	0	3 (1.0)	0	1 (0.3)	2 (0.6)
Related[c]	0	0	1 (0.3)	0	0	0
Severe	2 (0.7)	0	1 (0.3)	0	1 (0.3)	0
Life-threatening	0	0	0	0	0	1 (0.3)
Any nonserious adverse event	19 (6.2)	23 (7.6)	24 (7.8)	12 (3.9)	18 (5.9)	31 (9.8)
Related[c]	4 (1.3)	13 (4.3)	10 (3.3)	5 (1.6)	7 (2.3)	16 (5.1)
Severe	0	0	0	0	0	3 (0.9)
Life-threatening	0	0	0	0	0	0
Any adverse event leading to withdrawal	0	0	0	0	0	0
Related[c]	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0
Death	0	0	0	0	0	0

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to study intervention.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:30) Source Data: adae Table Generation: 12JUL2022 (23:33)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./ada2_sbe/C4591031_E_1MINEXP_EUA/adae_091_exp_cut

Adverse Events from Study Vaccination to 1 Month Post-Dose

An overview of AEs reported from study vaccination to 1-month post-Dose is shown in Table 42. In total, ≤10.4% of participants reported any AE after study vaccination across vaccine groups (range: 3.6% to 10.4%). AEs were generally reported at similar frequencies in the vaccine groups, except for

participants in the BA.1 30µg and Original/BA.1 30/30µg groups who reported AEs more frequently (8.5% and 10.4% respectively). Any related (per investigator assessment), SAEs, or severe AEs were reported by ≤5.1%, ≤1.0%, and ≤0.9% of participants, respectively. No withdrawals due to AEs or deaths were reported.

One (0.3%) participant in the Original/BA.1 30/30µg group reported a life-threatening (Grade 4) AE of atrial fibrillation.

Table 42. Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through 1 Month After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N[a]=305)	BNT162b2 (60 µg) (N[a]=302)	BNT162b2 OMI (30 µg) (N[a]=307)	BNT162b2 OMI (60 µg) (N[a]=306)	BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N[a]=305)	BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N[a]=316)
Adverse Event	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any adverse event	18 (5.9)	20 (6.6)	26 (8.5)	11 (3.6)	19 (6.2)	33 (10.4)
Related[c]	4 (1.3)	13 (4.3)	10 (3.3)	5 (1.6)	7 (2.3)	16 (5.1)
Severe	0	0	1 (0.3)	0	1 (0.3)	3 (0.9)
Life-threatening	0	0	0	0	0	1 (0.3)
Any serious adverse event	0	0	3 (1.0)	0	1 (0.3)	2 (0.6)
Related[c]	0	0	1 (0.3)	0	0	0
Severe	0	0	1 (0.3)	0	1 (0.3)	0
Life-threatening	0	0	0	0	0	1 (0.3)
Any nonserious adverse event	18 (5.9)	20 (6.6)	24 (7.8)	11 (3.6)	18 (5.9)	31 (9.8)

Adverse Event	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Related[c]	4 (1.3)	13 (4.3)	10 (3.3)	5 (1.6)	7 (2.3)	16 (5.1)
Severe	0	0	0	0	0	3 (0.9)
Life-threatening	0	0	0	0	0	0
Any adverse event leading to withdrawal	0	0	0	0	0	0
Related[c]	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0
Death	0	0	0	0	0	0

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to study intervention.
PFIZER CONFIDENTIAL SDTM Creation: 26MAY2022 (22:30) Source Data: adae Table Generation: 12JUL2022 (23:33)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2 ube/C4591031 E 1MINEXP EUA/adae 091 exp 1m

Subgroup Analyses

No clinically meaningful patterns within or between groups were noted regarding AE profiles, overall and categorically (i.e., related, or severe events) across all vaccine groups when evaluated by subgroups of sex, race, ethnicity and baseline SARS-CoV-2 status.

Subgroups of race (Black or African American, Asian), ethnicity (Hispanic/Latino), and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. While there were numerical differences between subgroups, there were no meaningful differences in the overall patterns of AEs by category across these subgroups. Subgroup data are summarized below.

Sex

The frequencies of AEs reported after study vaccination of Original (30-and 60-µg dose level) groups, BA.1 (30-and 60-µg dose level) groups, and Original/BA.1 (30-and 60-µg total dose level) groups in the sex subgroups of participants >55 years of age were:

		BNT162b2		BNT162b2 OMI		BNT162b2 + BNT162b2 OMI	
		30 µg	60 µg	30 µg	60 µg	30 µg	60 µg
	Male	n=145	n=145	n=154	n=153	n=162	n=153
	Female	n=160	n=157	n=153	n=153	n=143	n=163
AEs	Male	6.9%	4.1%	8.4%	2.6%	3.7%	9.2%
	Female	5.0%	8.9%	8.5%	4.6%	9.1%	11.7%
Related	Male	0.7%	2.8%	2.6%	2.0%	0.6%	3.9%
	Female	1.9%	5.7%	3.9%	1.3%	4.2%	6.1%
Severe	Male	0%	0%	0%	0%	0.6%	1.3%
	Female	0%	0%	0.7%	0%	0%	0.6%
Serious	Male	0%	0%	1.3%	0%	0.6%	0.7%
	Female	0%	0%	0.7%	0%	0%	0.6%

Race

The frequencies of AEs reported after study vaccination of Original (30-and 60-µg dose level) groups, BA.1 (30-and 60-µg dose level) groups, and Original/BA.1 (30-and 60-µg total dose level) groups in the race subgroups of participants >55 years of age were:

	BNT162b2		BNT162b2 OMI		BNT162b2 + BNT162b2 OMI	
	30 µg	60 µg	30 µg	60 µg	30 µg	60 µg
White	n=268	n=254	n=261	n=262	n=274	n=275
Black or African American	n=19	n=22	n=23	n=20	n=13	n=19
Asian	n=13	n=20	n=16	n=19	n=16	n=17
AEs						
White	6.0%	7.1%	9.2%	3.4%	6.9%	10.9%
Black or African American	10.5%	4.5%	8.7%	10.0%	0%	5.3%
Asian	0%	0%	0%	0%	0%	11.8%
Related						
White	1.1%	4.3%	3.4%	1.1%	2.6%	5.1%
Black or African American	5.3%	4.5%	4.3%	10.0%	0%	5.3%
Asian	0%	0%	0%	0%	0%	5.9%
Severe						
White	0%	0%	0.4%	0%	0.4%	1.1%
Black or African American	0%	0%	0%	0%	0%	0%
Asian	0%	0%	0%	0%	0%	0%
	BNT162b2		BNT162b2 OMI		BNT162b2 + BNT162b2 OMI	
Serious						
White	0%	0%	1.1%	0%	0.4%	0.4%
Black or African American	0%	0%	0%	0%	0%	0%
Asian	0%	0%	0%	0%	0%	5.9%

Ethnicity

The frequencies of AEs reported after study vaccination of Original (30-and 60-µg dose level) groups, BA.1 (30-and 60-µg dose level) groups, and Original/BA.1 (30-and 60-µg total dose level) groups in the ethnic subgroups of participants >55 years of age were:

	BNT162b2		BNT162b2 OMI		BNT162b2 + BNT162b2 OMI	
	30 µg	60 µg	30 µg	60 µg	30 µg	60 µg
Hispanic/Latino	n=57	n=38	n=44	n=46	n=45	n=44
Non-Hispanic/Non-Latino	n=248	n=264	n=263	n=260	n=260	n=272
AEs						
Hispanic/Latino	5.3%	0%	0%	4.3%	4.4%	6.8%
Non-Hispanic/Non-Latino	6.0%	7.6%	9.9%	3.5%	6.5%	11.0%
Related						
Hispanic/Latino	0%	0%	0%	2.2%	2.2%	4.5%
Non-Hispanic/Non-Latino	1.6%	4.9%	3.8%	1.5%	2.3%	5.1%
Severe						
Hispanic/Latino	0%	0%	0%	0%	0%	0%
Non-Hispanic/Non-Latino	0%	0%	0.4%	0%	0.4%	1.1%
Serious						
Hispanic/Latino	0%	0%	0%	0%	0%	0%
Non-Hispanic/Non-Latino	0%	0%	1.1%	0%	0.4%	0.7%

SARS-CoV-2 Baseline Status

The frequencies of AEs reported after study vaccination of Original (30-and 60-µg dose level) groups, BA.1 (30-and 60-µg dose level) groups, and Original/BA.1 (30-and 60-µg total dose level) groups in the SARS-CoV-2 baseline status subgroups were:

	BNT162b2		BNT162b2 OMI		BNT162b2 + BNT162b2 OMI	
	30 µg	60 µg	30 µg	60 µg	30 µg	60 µg
Baseline Positive	n=41	n=28	n=45	n=41	n=38	n=39
Baseline Negative	n=262	n=274	n=261	n=265	n=267	n=277
AEs						
Baseline Positive	4.9%	7.1%	13.3%	9.8%	2.6%	5.1%
Baseline Negative	6.1%	6.6%	7.7%	2.6%	6.7%	11.2%

	BNT162b2		BNT162b2 OMI		BNT162b2 + BNT162b2 OMI	
	30 µg	60 µg	30 µg	60 µg	30 µg	60 µg
Related						
Baseline Positive	2.4%	7.1%	4.4%	9.8%	0%	0%
Baseline Negative	1.1%	4.0%	3.1%	0.4%	2.6%	5.8%
Severe						
Baseline Positive	0%	0%	0%	0%	0%	0%
Baseline Negative	0%	0%	0.4%	0%	0.4%	1.1%
Serious						
Baseline Positive	0%	0%	0%	0%	0%	2.6%
Baseline Negative	0%	0%	1.1%	0%	0.4%	0.4%

Analysis of Adverse Events – expanded cohort

Adverse Events from Study Vaccination to 1 Month Post-Dose

Adverse Events by System Organ Class and Preferred Term 1 Month Post-Dose

AEs reported from study vaccination to 1-month post-Dose for participants across vaccine groups are presented in Table 43. Overall, frequencies of any AEs reported after study vaccination up to 1-month post-Dose were generally similar between groups (range: 3.6% to 10.4%), with AEs generally reported at similar frequencies in the vaccine groups, except for participants in the BA.1 30µg and Original/BA.1 30/30µg groups who reported AEs more frequently (8.5% and 10.4%).

Many AEs were consistent with reactogenicity events that were reported as AEs (e.g., injection site pain, diarrhoea, and pyrexia), which showed no clinically meaningful imbalance between groups. In the general disorders and administration site conditions SOC, AEs were reported at numerically higher incidence in most of the vaccine groups than the Original 30µg group (range: 0.3% to 2.8%), with the highest increases reported in participants in the Original 60µg and bivalent Original/BA.1 /30/30µg groups, largely attributable to injection site reactions and fatigue.

There were no reported events of myocarditis or pericarditis (protocol defined AESIs). Infections and illnesses typical of this age group were also reported with no clinically meaningful imbalance between groups. This AE profile is generally consistent with the known safety profile of Original 30µg.

Analysis of AEs from study vaccination to 1-month post-Dose did not suggest any safety concerns. Select AEs that were reported from study vaccination to 1-month post-Dose that merit additional detail to provide a fuller clinical picture according to the MAH are summarized below.

Palpitations: One male 65-74 years of age in the Original/BA.1 15/15µg, with onset on Day 1 post study vaccination and reported resolved within 4 days. The event was mild in severity (not SAE) and considered related to study intervention by the investigator.

Atrial fibrillation: Three participants reported SAEs of atrial fibrillation. These are discussed in detail in the section SAEs in the report below.

Additionally, a subset of AEs of clinical interest including lymphadenopathy and rashes are summarized in the section AEs of interest in the report below.

Table 43. Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through 1 Month After the Study Vaccination, by System Organ Class and Preferred Term – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)											
	BNT162b2 (30 µg) (N=505)		BNT162b2 (60 µg) (N=502)		BNT162b2 OMI (30 µg) (N=507)		BNT162b2 OMI (60 µg) (N=506)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N=505)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N=516)	
System Organ Class Preferred Term	n[a] (%)	(95% CI[b])	n[a] (%)	(95% CI[b])	n[a] (%)	(95% CI[b])	n[a] (%)	(95% CI[b])	n[a] (%)	(95% CI[b])	n[a] (%)	(95% CI[b])
Any adverse event	18 (3.5)	(2.1, 5.5)	33 (6.6)	(4.6, 9.1)	42 (8.3)	(6.0, 11.1)	19 (3.8)	(2.3, 5.9)	32 (6.3)	(4.4, 8.8)	38 (7.4)	(5.3, 10.0)
Blood and lymphatic system disorders	1 (0.2)	(0.0, 1.1)	5 (1.0)	(0.3, 2.3)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	2 (0.4)	(0.0, 1.4)
Lymphadenopathy	1 (0.2)	(0.0, 1.1)	5 (1.0)	(0.3, 2.3)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	2 (0.4)	(0.0, 1.4)
Cardiac disorders	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	2 (0.4)	(0.0, 1.4)
Atrial fibrillation	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	2 (0.4)	(0.0, 1.4)
Palpitations	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)
Ear and labyrinth disorders	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)
Middle ear inflammation	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)
Endocrine disorders	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)
Hypothyroidism	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)
Eye disorders	1 (0.2)	(0.0, 1.1)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)
Chalazion	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)
Ocular hyperaemia	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)
Vision blurred	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	0	(0.0, 0.7)
Vitreous degeneration	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)
Vitreous haemorrhage	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)
Gastrointestinal disorders	2 (0.4)	(0.0, 1.4)	0	(0.0, 0.7)	4 (0.8)	(0.2, 2.0)	0	(0.0, 0.7)	3 (0.6)	(0.1, 1.7)	2 (0.4)	(0.0, 1.4)
Diarrhoea	0	(0.0, 0.7)	0	(0.0, 0.7)	3 (0.6)	(0.1, 1.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)
Nausea	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)
Inguinal hernia	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)	0	(0.0, 0.7)
Abdominal distension	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	0	(0.0, 0.7)	1 (0.2)	(0.0, 1.1)

Constipation	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Gastrooesophageal reflux disease	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
General disorders and administration site conditions	1 (0.3)	(0.0, 1.8)	7 (2.3)	(0.9, 4.7)	5 (1.6)	(0.5, 3.8)	4 (1.3)	(0.4, 3.3)	5 (1.6)	(0.5, 3.8)	9 (2.8)	(1.3, 5.3)
Injection site pain	0	(0.0, 1.2)	4 (1.3)	(0.4, 3.4)	3 (1.0)	(0.2, 2.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	2 (0.6)	(0.1, 2.3)
Fatigue	0	(0.0, 1.2)	4 (1.3)	(0.4, 3.4)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	2 (0.6)	(0.1, 2.3)
Chills	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Injection site swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	2 (0.6)	(0.1, 2.3)
Pain	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Pyrexia	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Axillary pain	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Chest discomfort	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Injection site bruising	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Injection site pruritus	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Malaise	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Non-cardiac chest pain	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Swelling face	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vaccination site pain	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vaccination site swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Infections and infestations	2 (0.7)	(0.1, 2.3)	0	(0.0, 1.2)	4 (1.3)	(0.4, 3.3)	2 (0.7)	(0.1, 2.3)	3 (1.0)	(0.2, 2.8)	5 (1.6)	(0.5, 3.7)
Hordeolum	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)
Tooth infection	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Upper respiratory tract infection	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)
Conjunctivitis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Diverticulitis	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Localised infection	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Oral herpes	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Pneumonia	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Rocky mountain spotted fever	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Tonsillitis	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Tooth abscess	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Urinary tract infection	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vulvitis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Injury, poisoning and procedural complications	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	3 (0.9)	(0.2, 2.7)

Procedural pain	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Chemical burn	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Eye injury	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Joint injury	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Meniscus injury	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Muscle rupture	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Muscle strain	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Skin laceration	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Investigations	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Blood pressure increased	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Glycosylated haemoglobin increased	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Prostatic specific antigen increased	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Metabolism and nutrition disorders	2 (0.7)	(0.1, 2.3)	2 (0.7)	(0.1, 2.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Decreased appetite	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Dehydration	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Gout	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Hypercholesterolaemia	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Hyperlipidaemia	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Musculoskeletal and connective tissue disorders	4 (1.3)	(0.4, 3.3)	3 (1.0)	(0.2, 2.9)	2 (0.7)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)	6 (2.0)	(0.7, 4.2)	3 (0.9)	(0.2, 2.7)
Myalgia	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	3 (1.0)	(0.2, 2.8)	2 (0.6)	(0.1, 2.3)
Arthralgia	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	0	(0.0, 1.2)
Back pain	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Neck pain	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Ankylosing spondylitis	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Arthritis	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Muscular weakness	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Osteoporosis	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Pain in extremity	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	2 (0.6)	(0.1, 2.3)
Breast cancer	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Cholesteatoma	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Hypergammaglobulinaemia benign monoclonal	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Parathyroid tumour benign	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)

Polycythaemia vera	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Prostate cancer	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Squamous cell carcinoma	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Nervous system disorders	3 (1.0)	(0.2, 2.8)	4 (1.3)	(0.4, 3.4)	4 (1.3)	(0.4, 3.3)	2 (0.7)	(0.1, 2.3)	6 (2.0)	(0.7, 4.2)	2 (0.6)	(0.1, 2.3)
Headache	0	(0.0, 1.2)	2 (0.7)	(0.1, 2.4)	2 (0.7)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)	4 (1.3)	(0.4, 3.3)	2 (0.6)	(0.1, 2.3)
Dizziness	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.2)
Loss of consciousness	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Morton's neuralgia	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Restless legs syndrome	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Somnolence	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Syncope	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Transient ischaemic attack	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Tremor	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Renal and urinary disorders	2 (0.7)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Dysuria	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Hypertonic bladder	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Micturition urgency	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Nephrolithiasis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Pollakiuria	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Renal cyst	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Urinary retention	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Reproductive system and breast disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Scrotal swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Obstructive sleep apnoea syndrome	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Skin and subcutaneous tissue disorders	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.4)	2 (0.7)	(0.1, 2.3)	0	(0.0, 1.2)	0	(0.0, 1.2)	4 (1.3)	(0.3, 3.2)
Rash	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	3 (0.9)	(0.2, 2.7)
Dermatitis contact	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Lichenoid keratosis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Psoriasis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Urticaria	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)

Vascular disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Flushing	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Hypertension	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any 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: 26MAY2022 (22:30) Source Data: adae Table Generation: 12JUL2022 (23:33)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2 ube/C4591031 E 1MINEXP EUA/adae 130 exp 1m

Subgroup Analyses 1 month post Dose

Subgroups of participants >55 years of age in the safety population had generally similar AE profiles from study vaccination to 1-month post-Dose, across various vaccine groups when evaluated by subgroups of sex, race, ethnicity and baseline SARS-CoV-2 status. Subgroups of race (Black or African American, Asian), ethnicity (Hispanic/Latino) and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution.

In general, the AE profiles within each subgroup were similar to the overall AE profile for the safety population as whole, reflecting events consistent with reactogenicity and other illnesses that are commonly reported in the general population >55 years of age. While there were numerical differences between subgroups, there were no meaningful differences in the overall patterns of AEs by category across these subgroups.

Related Adverse Events 1-month post-Dose

From study vaccination to 1-month post-Dose, AEs assessed by the investigator as related to study intervention were reported with generally similar frequencies between groups. Incidence of related AEs were numerically higher in the Original 60µg (4.3%), BA.1 30µg (3.3%), and Original/BA.1 30/30µg (5.1%) groups (Table 44).

Most related AEs were consistent with reactogenicity events and in the SOC of general disorders and administration site conditions (range: 0.3% to 2.3%). Related AEs of clinical interest (e.g., lymphadenopathy, rashes, arthritis) are included in the AESI analysis further below.

Table 44. Number (%) of Participants Reporting at Least 1 Related Adverse Event From the Study Vaccination Through 1 Month After the Study Vaccination, by System Organ Class and Preferred Term – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)											
	BNT162b2 (30 µg) (N=505)		BNT162b2 (60 µg) (N=502)		BNT162b2 OMI (30 µg) (N=507)		BNT162b2 OMI (60 µg) (N=506)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N=505)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N=516)	
System Organ Class Preferred Term	n[a] (%)	(95% CI)	n[a] (%)	(95% CI)	n[a] (%)	(95% CI)	n[a] (%)	(95% CI)	n[a] (%)	(95% CI)	n[a] (%)	(95% CI)
Any adverse event	4 (1.3)	(0.4, 3.3)	13 (4.3)	(2.3, 7.2)	10 (3.3)	(1.6, 5.9)	5 (1.6)	(0.5, 3.8)	7 (2.3)	(0.9, 4.7)	16 (5.1)	(2.9, 8.1)
Blood and lymphatic system disorders	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.9)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	2 (0.6)	(0.1, 2.3)
Lymphadenopathy	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.9)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	2 (0.6)	(0.1, 2.3)
Cardiac disorders	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Atrial fibrillation	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Palpitations	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Eye disorders	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Ocular hyperaemia	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vision blurred	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Gastrointestinal disorders	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	4 (1.3)	(0.4, 3.3)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Diarrhoea	0	(0.0, 1.2)	0	(0.0, 1.2)	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Nausea	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
General disorders and administration site conditions	1 (0.3)	(0.0, 1.8)	7 (2.3)	(0.9, 4.7)	5 (1.6)	(0.5, 3.8)	4 (1.3)	(0.4, 3.3)	4 (1.3)	(0.4, 3.3)	7 (2.2)	(0.9, 4.5)
Injection site pain	0	(0.0, 1.2)	4 (1.3)	(0.4, 3.4)	3 (1.0)	(0.2, 2.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	2 (0.6)	(0.1, 2.3)
Fatigue	0	(0.0, 1.2)	4 (1.3)	(0.4, 3.4)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)
Chills	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Injection site swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	2 (0.6)	(0.1, 2.3)
Pain	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Pyrexia	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Axillary pain	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Chest discomfort	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Injection site bruising	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Injection site pruritus	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)

Malaise	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Swelling face	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vaccination site pain	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vaccination site swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Injury, poisoning and procedural complications	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Joint injury	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Metabolism and nutrition disorders	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Decreased appetite	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Dehydration	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Musculoskeletal and connective tissue disorders	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	3 (1.0)	(0.2, 2.8)	3 (0.9)	(0.2, 2.7)
Myalgia	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	2 (0.7)	(0.1, 2.3)	2 (0.6)	(0.1, 2.3)
Neck pain	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Arthralgia	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Muscular weakness	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Nervous system disorders	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.9)	2 (0.7)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.8)	1 (0.3)	(0.0, 1.8)
Headache	0	(0.0, 1.2)	2 (0.7)	(0.1, 2.4)	2 (0.7)	(0.1, 2.3)	0	(0.0, 1.2)	3 (1.0)	(0.2, 2.8)	1 (0.3)	(0.0, 1.8)
Dizziness	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Renal and urinary disorders	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Pollakiuria	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Skin and subcutaneous tissue disorders	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	4 (1.3)	(0.3, 3.2)
Rash	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	3 (0.9)	(0.2, 2.7)
Urticaria	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)

System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any 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: 26MAY2022 (22:30) Source Data: adae Table Generation: 12JUL2022 (23:34)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2_ube/C4591031_E_1MINEXP_EUA/adae_130_exp_rel_1m

Immediate Adverse Events

No immediate AEs (occurring within 30 minutes post-vaccination) were reported after study vaccination for any of the vaccine groups.

Severe and Life-Threatening Adverse Events 1-month post-Dose

Severe AEs from study vaccination through 1-month post-Dose are presented in Table 45.

Table 45. Number (%) of Participants Reporting at Least 1 Severe Adverse Event From the Study Vaccination Through 1 Month After the Study Vaccination, by System Organ Class and Preferred Term – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)											
	BNT162b2 (30 µg) (N[a]=305)		BNT162b2 (60 µg) (N[a]=302)		BNT162b2 OMI (30 µg) (N[a]=307)		BNT162b2 OMI (60 µg) (N[a]=306)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N[a]=305)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N[a]=316)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	3 (0.9)	(0.2, 2.7)
Gastrointestinal disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Gastrooesophageal reflux disease	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
General disorders and administration site conditions	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Injection site swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Metabolism and nutrition disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Dehydration	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Musculoskeletal and connective tissue disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Muscular weakness	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Nervous system disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Headache	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any 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: 26MAY2022 (22:30) Source Data: adae Table Generation: 12JUL2022 (23:33)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: /ads2 ube/C4591031 E 1MINEXP EUA/adae 130 exp sev 1m

No participants in the Original 30- or 60-µg groups or in the BA.1 60-µg group reported severe AEs from study vaccination through 1-month post-Dose.

From study vaccination through 1-month post-Dose, 1 (0.3%) participant in the Original/BA.1 15/15µg-group reported a severe AE of gastroesophageal reflux disease. This event was considered as not related to study intervention by the investigator and is summarized below:

Participant (≥75-year-old male)

This case concerned an ≥75-year-old male, who experienced gastroesophageal reflux 27 days after receiving Dose one study vaccine (Original/BA.1 15/15µg) with the duration of 4 days. This was by the investigator assessed as not related to study vaccine and as not an SAE or immediate AE.

From study vaccination through 1-month post-Dose, 1 (0.3%) participant in the BA.1 30-µg group reported a severe AE of dehydration. This event was also reported as a SAE and considered related to study intervention by the investigator and is summarized below:

Participant (≥75-year-old female)

This medically confirmed case concerned a ≥75-year-old female who experienced dehydration on 2 days after receiving Dose 1 (BA.1 30 µg). On the morning of Day 2, the participant experienced fatigue, generalized malaise, myalgia, arthralgia, severe headache, and diarrhoea. On Day 3, the symptoms persisted, and the participant reported feeling "maybe a little shortness of breath," but denied experiencing chest pain, dizziness/syncope, or referred pain. The participant reported feeling her heart suddenly "pounding" while cleaning. The participant was diagnosed with dehydration by her primary care provider, and she presented to the emergency room (ER) for rehydration. At the ER, the

participant was tachycardic (heart rate o188 beats/min) and was hospitalized because of heart palpitations, tachycardia, and dehydration associated with a "tight and swollen" throat and dyspnea. An electrocardiogram was normal. Laboratory test results showed white blood cell count of 3.6 k/µL (normal range [NR]: 4.5-11 k/µL), red cell distribution width of 16.1% (NR: 11.5%-15%), absolute lymphocyte count of 0.5 k/µL (NR: 1.0-4.8 k/µL), glucose of 150 mg/dL (NR: 70-99 mg/dL), total bilirubin of 1.3 mg/dL (NR: 0.3-1.0 mg/dL), neutrophils of 79.6% (NR: 40%-75%). Acute cardiac events were ruled out. The participant was diagnosed with pneumonia (assessed by the investigator as nonserious event, not related to study vaccine) and was treated with IV azithromycin 500 mg once on (Day 3) and the dose was given orally once daily on Days 4 to 7. On Day 4, the dehydration resolved, and the participant was discharged from the hospital. On Day 7, the pneumonia resolved. On Day 12 during a follow-up visit, the participant was in a normal state of health and denied any reoccurrence of symptoms or any acute respiratory symptoms. On the same day (Day 12), the diarrhoea was considered resolved. In the opinion of the investigator, there was a reasonable possibility that the dehydration was related to the study intervention but was not related to concomitant medications or clinical trial procedures. MAH concurred with the investigator's causality assessment.

Three (0.9%) participants in the Original/BA.1 30/30µg group reported severe AEs of injection site swelling, headache, and muscle weakness (1 participant each).

Adverse Events from Study Vaccination to Data Cutoff Date

Few additional AEs were reported from study vaccination from post-Dose to the data cutoff date (16 May 2022) for participants in the Original 30µg (6.6% vs 5.9%) Original 60µg (7.6% vs 6.6%), and BA.1 60µg (3.9% vs 3.6%) groups (Table 20). Overall, frequencies of any AEs reported after study vaccination up the data cutoff date were generally similar between vaccine groups. Many of the AEs were consistent with reactogenicity events (e.g., pyrexia, and fatigue). Overall, all but one (non-SAE case with injection site pain) of the additional AEs and SAEs reported after 1-month post-Dose up to the data cutoff date consisted of unrelated events and 2 of them were reported as SAEs: ischaemic stroke and pneumonia described in short below:

Participant (55 – 64-year-old male)

A 55 - 64-year-old male with a medical history of type 2 diabetes mellitus, obesity, and memory loss, received Dose 1 Original 30µg. Concomitant medications included insulin for diabetes mellitus, alendronate for osteoporosis, famotidine, metformin for diabetes mellitus, and memantine for amnesia. The participant was diagnosed with acute ischemic stroke. 33 days after receiving Dose 1. At Day 33 the participant woke up with a stroke alert for global aphasia and mild dysarthria and was taken to the hospital. A brain computed tomography (CT) showed no haemorrhage and a CT angiogram without contrast showed no large vessel occlusion; however, mild to moderate left internal carotid atherosclerosis was noted, therefore endovascular therapy was ruled out. A repeat scan after 24 hours was stable, and the National Institutes of Health Stroke Scale score was 1. An echocardiogram revealed good ejection fraction without a shunt. On the same day (Day 33), the participant had hypertension (blood pressure readings were not reported). The diagnosis of acute ischemic stroke was confirmed. During hospitalization, the participant received ondansetron, acetylsalicylic acid, candesartan, rosuvastatin, and bumetanide (all for 33 days after receiving Dose 1). On Day 35, the ischemic stroke and hypertension were considered resolved, and the participant was discharged from the hospital. In the opinion of the investigator, there was no reasonable possibility that the ischemic stroke was related to the study intervention, concomitant medications, or clinical trial procedures. The MAH concurred with the investigator's causality assessment, and considered that the participant's underlying diseases, including obesity, diabetes, and hypertension, were considered as high-risk factors for the ischemic stroke.

Participant (55 - 64-year-old male)

A 55 – 64-year-old male was diagnosed and reported with an unrelated severe (Grade 3) pneumonia 46 days after receiving Dose 1 (Original 30µg), reported as continuing at the data cutoff date. It is unknown if the event has resolved, and no further clinical information is available.

Table 46. Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through Cutoff Date, by System Organ Class and Preferred Term – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)											
	BNT162b2 (30 µg) (N[a]=305)		BNT162b2 (60 µg) (N[a]=302)		BNT162b2 OMI (30 µg) (N[a]=307)		BNT162b2 OMI (60 µg) (N[a]=306)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N[a]=305)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N[a]=316)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	20 (6.6)	(4.1, 9.9)	23 (7.6)	(4.9, 11.2)	26 (8.5)	(5.6, 12.2)	12 (3.9)	(2.0, 6.7)	19 (6.2)	(3.8, 9.6)	33 (10.4)	(7.3, 14.4)
Blood and lymphatic system disorders	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.9)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	2 (0.6)	(0.1, 2.3)
Lymphadenopathy	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.9)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	2 (0.6)	(0.1, 2.3)
Cardiac disorders	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	2 (0.6)	(0.1, 2.3)
Atrial fibrillation	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	2 (0.6)	(0.1, 2.3)
Palpitations	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Ear and labyrinth disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Middle ear inflammation	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Endocrine disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Hypothyroidism	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Eye disorders	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Chalazion	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Ocular hyperaemia	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vision blurred	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vitreous degeneration	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vitreous haemorrhage	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Gastrointestinal disorders	2 (0.7)	(0.1, 2.3)	0	(0.0, 1.2)	4 (1.3)	(0.4, 3.3)	0	(0.0, 1.2)	3 (1.0)	(0.2, 2.8)	2 (0.6)	(0.1, 2.3)
Diarrhoea	0	(0.0, 1.2)	0	(0.0, 1.2)	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Nausea	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Inguinal hernia	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Abdominal distension	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Constipation	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)

Gastrooesophageal reflux disease	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
General disorders and administration site conditions	1 (0.3)	(0.0, 1.8)	7 (2.3)	(0.9, 4.7)	5 (1.6)	(0.5, 3.8)	4 (1.3)	(0.4, 3.3)	5 (1.6)	(0.5, 3.8)	9 (2.8)	(1.3, 5.3)
Injection site pain	0	(0.0, 1.2)	4 (1.3)	(0.4, 3.4)	3 (1.0)	(0.2, 2.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	2 (0.6)	(0.1, 2.3)
Fatigue	0	(0.0, 1.2)	4 (1.3)	(0.4, 3.4)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	2 (0.6)	(0.1, 2.3)
Chills	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Injection site swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	2 (0.6)	(0.1, 2.3)
Pain	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Pyrexia	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Axillary pain	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Chest discomfort	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Injection site bruising	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Injection site pruritus	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Malaise	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Non-cardiac chest pain	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Swelling face	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vaccination site pain	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vaccination site swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Infections and infestations	3 (1.0)	(0.2, 2.8)	1 (0.3)	(0.0, 1.8)	4 (1.3)	(0.4, 3.3)	2 (0.7)	(0.1, 2.3)	3 (1.0)	(0.2, 2.8)	5 (1.6)	(0.5, 3.7)
Hordeolum	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)
Pneumonia	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Tooth infection	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Upper respiratory tract infection	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)
Urinary tract infection	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Conjunctivitis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Diverticulitis	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Localised infection	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Oral herpes	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Rocky mountain spotted fever	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Tonsillitis	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Tooth abscess	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Vulvitis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Injury, poisoning and procedural complications	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	3 (0.9)	(0.2, 2.7)
Procedural pain	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Chemical burn	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Eye injury	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)

Joint injury	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Meniscus injury	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Muscle rupture	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Muscle strain	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Skin laceration	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Investigations	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Blood pressure increased	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Glycosylated haemoglobin increased	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Prostatic specific antigen increased	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Metabolism and nutrition disorders	2 (0.7)	(0.1, 2.3)	2 (0.7)	(0.1, 2.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Decreased appetite	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Dehydration	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Gout	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Hypercholesterolaemia	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Hyperlipidaemia	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Musculoskeletal and connective tissue disorders	4 (1.3)	(0.4, 3.3)	4 (1.3)	(0.4, 3.4)	2 (0.7)	(0.1, 2.3)	2 (0.7)	(0.1, 2.3)	6 (2.0)	(0.7, 4.2)	3 (0.9)	(0.2, 2.7)
Myalgia	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	3 (1.0)	(0.2, 2.8)	2 (0.6)	(0.1, 2.3)
Arthralgia	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	0	(0.0, 1.2)
Back pain	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Neck pain	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Ankylosing spondylitis	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Arthritis	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Bursitis	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Muscular weakness	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Osteoarthritis	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Osteoporosis	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Pain in extremity	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Spinal osteoarthritis	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	2 (0.6)	(0.1, 2.3)
Breast cancer	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Cholesteatoma	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Hypergammaglobulinaemia benign monoclonal	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Parathyroid tumour benign	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Polycythaemia vera	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Prostate cancer	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)

Squamous cell carcinoma	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Nervous system disorders	4 (1.3)	(0.4, 3.3)	4 (1.3)	(0.4, 3.4)	4 (1.3)	(0.4, 3.3)	2 (0.7)	(0.1, 2.3)	6 (2.0)	(0.7, 4.2)	2 (0.6)	(0.1, 2.3)
Headache	0	(0.0, 1.2)	2 (0.7)	(0.1, 2.4)	2 (0.7)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)	4 (1.3)	(0.4, 3.3)	2 (0.6)	(0.1, 2.3)
Dizziness	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.2)
Ischaemic stroke	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Loss of consciousness	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Morton's neuralgia	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Restless legs syndrome	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Somnolence	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Syncope	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Transient ischaemic attack	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Tremor	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Renal and urinary disorders	2 (0.7)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Dysuria	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Hypertonic bladder	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Micturition urgency	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Nephrolithiasis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Pollakiuria	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Renal cyst	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Urinary retention	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Reproductive system and breast disorders	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Breast tenderness	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Scrotal swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Obstructive sleep apnoea syndrome	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Skin and subcutaneous tissue disorders	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.4)	2 (0.7)	(0.1, 2.3)	0	(0.0, 1.2)	0	(0.0, 1.2)	4 (1.3)	(0.3, 3.2)
Rash	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	3 (0.9)	(0.2, 2.7)
Dermatitis contact	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Lichenoid keratosis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Psoriasis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Urticaria	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Surgical and medical procedures	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Tooth extraction	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)

Vascular disorders	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Hypertension	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Flushing	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any 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: 26MAY2022 (22:30) Source Data: adae Table Generation: 12JUL2022 (23:33)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2_ube/C4591031_E_1MINEXP_EUA/adae_130_cut_exp_1m

Deaths

No participants died between study vaccination to the data cutoff date of 16 May 2022

Serious Adverse Events

Summary and Analysis of SAEs from Study Vaccination to Data Cutoff Date

Few SAEs were reported among participants across the vaccine groups evaluated from study vaccination to 1-month post-Dose (n=6) and to the data cutoff date additional 2 cases (16 May 2022) (Table 23). One SAE of dehydration in the BA.1 30µg group was considered to be related to study intervention by the investigator. SAEs are summarized below.

Original 30µg group:

Participant (55 – 64 -year-old male)

Reported with an unrelated severe (Grade 3) SAE of pneumonia with onset 46 days post-Dose that was reported as continuing at the data cutoff date.

Participant (55- 64 -year-old male)

Reported with an unrelated severe (Grade 3) SAE of ischaemic stroke concurrent with an unrelated AE of hypertension with onset 33 days post-Dose that was reported as resolved within 3 days.

BA.1 30µg group:

Participant (≥75-year-old female)

Reported with a related severe (Grade 3) SAE of dehydration concurrent with nonserious AE of skin laceration (unrelated) and diarrhoea (related) with onset on Day 2 post-vaccination and resolved within 3 days (except for skin laceration which was reported as continuing at data cutoff date, and diarrhoea which resolved within 11 days). This participant also reported a nonserious AE of pneumonia (unrelated) with onset on Day 3 post-vaccination and reported as resolved within 5 days.

Participant (≥75-year-old male)

Reported with an unrelated mild SAE (Grade 1) of prostate cancer on Day 11 post-Dose that was reported as continuing at the data cutoff date.

Participant (≥75-year-old male)

Reported an unrelated SAE of nephrolithiasis (left renal calculi, Grade 2) on Day 26 post-Dose that was reported as continuing at the data cutoff date.

Original/BA.1 15/15µg group:

Participant (≥75-year-old male)

Reported with an unrelated severe (Grade 3) SAE of gastrooesophageal reflux on Day 27 post-vaccination that was reported as resolved within 4 days.

Original/BA.1 30/30µg group:

Participant (≥75-year-old male)

Reported with an unrelated SAE (Grade 4) of atrial fibrillation on Day 1 of study vaccination that resolved within 4 days and considered not related to study intervention by the investigator. This participant had a medical history of type 2 diabetes, hyperlipidemia, hypercholesterolemia, coronary artery disease including 5-vessel bypass, hypertension, coronary artery bypass graft and hypertension.

Participant (≥75-year-old female)

Reported with an unrelated SAE (Grade 1) of atrial fibrillation on Day 28 of study vaccination that resolved within 1 day and considered not related to study intervention by the investigator. This participant had a medical history of atrial fibrillation.

Table 47. Number (%) of Participants Reporting at Least 1 Serious Adverse Event From the Study Vaccination Through Cutoff Date, by System Organ Class and Preferred Term – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)											
	BNT162b2 (30 µg) (N[a]=305)		BNT162b2 (60 µg) (N[a]=302)		BNT162b2 OMI (30 µg) (N[a]=307)		BNT162b2 OMI (60 µg) (N[a]=306)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N[a]=305)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N[a]=316)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	2 (0.7)	(0.1, 2.3)	0	(0.0, 1.2)	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	2 (0.6)	(0.1, 2.3)
Cardiac disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	2 (0.6)	(0.1, 2.3)
Atrial fibrillation	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	2 (0.6)	(0.1, 2.3)
Gastrointestinal disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Gastrooesophageal reflux disease	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Infections and infestations	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Pneumonia	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Metabolism and nutrition disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Dehydration	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Prostate cancer	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Nervous system disorders	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Ischaemic stroke	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Renal and urinary disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Nephrolithiasis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any 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: 26MAY2022 (22:30) Source Data: adae Table Generation: 12JUL2022 (23:33)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2 ube/C4591031 E 1MINEXP EUA/adae 130 cut ser exp 1m

Discontinuations from Study Intervention or Study Due to Adverse Events

No participants in the study discontinued due to AEs from study vaccination to the data cutoff date of 16 May 2022.

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, which includes AEs of special interest that have been requested by FDA to be analysed.

As of the data cutoff date (16 May 2022) there were no cases reported of myocarditis/pericarditis, Bell's palsy (or facial paralysis/paresis), appendicitis, or vaccine related anaphylaxis. AEs of clinical interest that were identified in the safety database as of the data cutoff date included lymphadenopathy, arthritis and rash, which are summarized below.

Lymphadenopathy

Lymphadenopathy is considered an adverse reaction to the reference vaccine and is noted as such in the product labelling. From study vaccination to data cutoff date, the incidence of lymphadenopathy was 0.4% (range 0 to 1.0%) across vaccine groups evaluated (Table 21).

All 8 events were considered by the investigator as related to study intervention. All cases were mild to moderate in severity, occurred generally within 1 to 4 days post-Dose, were located in the axillae and most resolved within 2 to 8 days. Additionally, 1 (0.3%) participant in the Original/BA.1 30/30µg group reported axillary pain (Grade 1, assessed as related) (Table 21). This event occurred on Day 2 post-Dose and was resolved within 3 days.

Rash

Rash is considered an adverse reaction to the reference vaccine and is noted as such in the product labelling. From study vaccination to data cutoff date, 4 participants reported a rash after study vaccination (Table 24). All events of rash were mild and considered by the investigator as related to study intervention, most events occurred on Day 2 or 3 post vaccination and resolved within 2 to 9 days after onset.

One participant in the Original/BA.1 30/30µg group reported a mild event of urticaria on Day 4 post vaccination that was reported as resolved within 10 days and considered to be related to study intervention by the investigator.

One participant in the BA.1 30µg reported a mild related event of injection site pruritus on Day 4 post vaccination that was reported as resolved within 8 days.

Chest Pain

Participant (55-64-year-old)

One (0.3%) participant in the Original 30µg group reported a nonserious AE of chest discomfort (Table 24). This participant reported a nonserious event of chest discomfort of moderate severity on Day 2 post study vaccination that resolved within 28 days with no other symptoms. The investigator considered the event as related to study intervention. Troponin levels reported at the cardiac illness visit were <3 ng/L (reference range: 0-47 ng/L) and ECG was reported as normal. The participant had no other reported AEs and had a medical history of type 2 diabetes, diabetic neuropathy, hypertension and hyperlipidemia.

Arthritis

Participant (65 - 74-year-old male)

Arthritis (joint inflammation, mild in severity) was reported in a male in the Original 30µg group with onset at day 10 post-Dose. This participant had a medical history of osteoarthritis () and spinal osteoarthritis, knee arthroplasty, and joint range of motion decreased, received Dose 1 (Original 30µg) and experienced arthritis, 9 days after receiving Dose 1. The participant engaged in intense physical activity a week prior to the onset of the arthritis. The arthritis was ongoing at the time of the last available report.

Participant (65-74-year-old female)

Additionally, ankylosing spondylitis (worsening of ankylosing spondylitis, mild in severity) was reported in a female participant in the Original/BA.1 15/15µg group with onset of 10 days post-Dose and reported as continuing at the time of data cutoff date. Both events were considered not related to study intervention by the study physician.

Angioedema:

Participant (65-74-year-old female)

A female with a medical history of hypercholesterolemia, received Dose 1 developed angioedema, 17 days after receiving Dose 1 (BA.1 30µg). On Day 25 after dose, the angioedema of the face of unknown aetiology resolved. On Day 28 after dose, the participant developed swelling, which was ongoing at the time of the last available report. In the opinion of the study physician, there was no reasonable possibility that the angioedema was related to the study intervention.

No other AEs were reported by either participant.

Table 48. Number (%) of Participants Reporting at Least 1 Adverse Event of Special Interest From the Study Vaccination Through 1 Month After the Study Vaccination, by System Organ Class and Preferred Term – Expanded Cohort – Participants >55 Years of Age – Safety Population

	Vaccine Group (as Administered)											
	BNT162b2 (30 µg) (N[a]=305)		BNT162b2 (60 µg) (N[a]=302)		BNT162b2 OMI (30 µg) (N[a]=307)		BNT162b2 OMI (60 µg) (N[a]=306)		BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N[a]=305)		BNT162b2 (30 µg) + BNT162b2 OMI (30 µg) (N[a]=316)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	4 (1.3)	(0.4, 3.3)	3 (1.0)	(0.2, 2.9)	5 (1.6)	(0.5, 3.8)	3 (1.0)	(0.2, 2.8)	3 (1.0)	(0.2, 2.8)	8 (2.5)	(1.1, 4.9)
Endocrine disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Hypothyroidism	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Eye disorders	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Ocular hyperaemia	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Vitreous haemorrhage	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
General disorders and administration site conditions	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	2 (0.6)	(0.1, 2.3)
Pyrexia	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Chest discomfort	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Injection site bruising	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Swelling	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Swelling face	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Infections and infestations	0	(0.0, 1.2)	0	(0.0, 1.2)	2 (0.7)	(0.1, 2.3)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Oral herpes	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Pneumonia	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Musculoskeletal and connective tissue disorders	2 (0.7)	(0.1, 2.3)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.2)
Arthralgia	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)	0	(0.0, 1.2)
Ankylosing spondylitis	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Arthritis	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Hypergammaglobulinaemia benign monoclonal	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Skin and subcutaneous tissue disorders	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	4 (1.3)	(0.3, 3.2)
Rash	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	3 (0.9)	(0.2, 2.7)
Psoriasis	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)
Urticaria	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Vascular disorders	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)
Flushing	0	(0.0, 1.2)	0	(0.0, 1.2)	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)	0	(0.0, 1.2)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any 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: 26MAY2022 (22:30) Source Data: adae Table Generation: 12JUL2022 (23:33)
(Data cutoff date : 16MAY2022 Database snapshot date : 26MAY2022) Output File: ./nda2_ube/C4591031_E_1MINEXP_EUA/adae_130_exp_aesi_1m

Other Safety Evaluations

Severe COVID-19 Illness

No severe cases of COVID-19 following study vaccination were reported as of the data cutoff date (16 May 2022).

Pregnancy

Pregnancies were reported as exposure during pregnancies (EDPs) if occurring in a participant or participant's partner within 28 days after last dose of study intervention. There were no EDPs reported during the protocol-specified window as of the data cutoff date.

Surveillance of COVID-19 Cases – Expanded Cohort

COVID-19 Cases up to Data Cutoff Date

In the expanded cohort, cases in a total of 30 participants across all vaccine groups were accrued up to the data cutoff date of 16 May 2022.

- Original 30µg and 60µg groups: 7 and 6 cases, respectively
- BA.1 30µg and 60µg groups: 7 and 3 cases, respectively
- Original/BA.1 15/15µg and 30/30µg groups: 1 and 6 cases, respectively.

Most cases (n=29) met both protocol-defined and CDC defined criteria for COVID-19 disease. One case in the Original/BA.1 30/30µg group met only the CDC-defined criteria. The reported signs and symptoms were generally similar for participants in the different studied vaccine groups, and the most commonly reported were new or increased cough (n=19) and sore throat (n=19). Few participants reported >3 concurrent signs and symptoms (n=8).

No cases meeting severe criteria per the FDA or CDC definition were observed in any of the vaccine groups.

5.3 Results - C4591031 Substudy D

5.3.1 Disposition and demographics

Disposition

No participants were excluded from the safety population, which included a total of 640 participants: 315 in the BA.1 30µg group and 325 in the Original 30µg group (Table 49).

Table 49. Safety Population – Cohort 2

	Vaccine Group (as Administered)		
	BNT162b2 OMI (30 µg) n[a]	BNT162b2 (30 µg)) n[a]	Total n[a] (%)
Randomized[b]			640
Vaccinated	315	325	640 (100.0)
Safety population	315	325	640 (100.0)
HIV-positive	1	0	1 (0.2)
Excluded from safety population			0

Abbreviation: HIV = human immunodeficiency virus.
a. n = Number of participants with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 11APR2022 (01:32) Source Data: adsl Table Generation: 18MAY2022 (01:46)
(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File:

Demographics

Table 50. Demographic Characteristics – Cohort 2 - Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 OMI (30 µg) (N[a]=315) n[b] (%)	BNT162b2 (30 µg) (N[a]=325) n[b] (%)	Total (N[a]=640) n[b] (%)
Sex			
Male	163 (51.7)	168 (51.7)	331 (51.7)
Female	152 (48.3)	157 (48.3)	309 (48.3)
Race			
White	237 (75.2)	227 (69.8)	464 (72.5)
Black or African American	21 (6.7)	34 (10.5)	55 (8.6)
American Indian or Alaska Native	1 (0.3)	4 (1.2)	5 (0.8)
Asian	42 (13.3)	45 (13.8)	87 (13.6)
Native Hawaiian or other Pacific Islander	2 (0.6)	3 (0.9)	5 (0.8)
Multiracial	10 (3.2)	11 (3.4)	21 (3.3)
Not reported	2 (0.6)	1 (0.3)	3 (0.5)
Ethnicity			
Hispanic/Latino	48 (15.2)	46 (14.2)	94 (14.7)
Non-Hispanic/non-Latino	266 (84.4)	279 (85.8)	545 (85.2)

Not reported	1 (0.3)	0	1 (0.2)
Country			
USA	315 (100.0)	325 (100.0)	640 (100.0)
Age group (at first study vaccination)			
18-30 Years	40 (12.7)	44 (13.5)	84 (13.1)
31-55 Years	275 (87.3)	281 (86.5)	556 (86.9)
Age at first study vaccination (years)			
Mean (SD)	41.8 (9.33)	42.4 (9.06)	42.1 (9.19)
Median	43.0	44.0	43.0
Min, max	(18, 55)	(19, 55)	(18, 55)
Time (months) from Dose 3 of BNT162b2 (received prior to the study) to first study vaccination			
n	314	325	639
Mean (SD)	4.3 (1.01)	4.2 (0.96)	4.3 (0.98)
Median	4.0	4.0	4.0
Min, max	(3.3, 6.8)	(3.3, 6.6)	(3.3, 6.8)
<3 Months	0	0	0
3 to <4 Months	164 (52.1)	162 (49.8)	326 (50.9)
4 to <5 Months	97 (30.8)	113 (34.8)	210 (32.8)
5 to <6 Months	0	0	0
≥6 Months	53 (16.8)	50 (15.4)	103 (16.1)
Missing	1 (0.3)	0	1 (0.2)
Baseline SARS-CoV-2 status			
Positive[c]	56 (17.8)	53 (16.3)	109 (17.0)
Positive NAAT	14 (4.4)	11 (3.4)	25 (3.9)
Negative[d]	259 (82.2)	272 (83.7)	531 (83.0)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	5 (1.6)	2 (0.6)	7 (1.1)
Normal weight (≥18.5-24.9 kg/m^2)	90 (28.6)	91 (28.0)	181 (28.3)
Overweight (≥25.0-29.9 kg/m^2)	85 (27.0)	111 (34.2)	196 (30.6)
Obese (≥30.0 kg/m^2)	135 (42.9)	121 (37.2)	256 (40.0)

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

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.

b. n = Number of participants with the specified characteristic.

c. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.

d. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

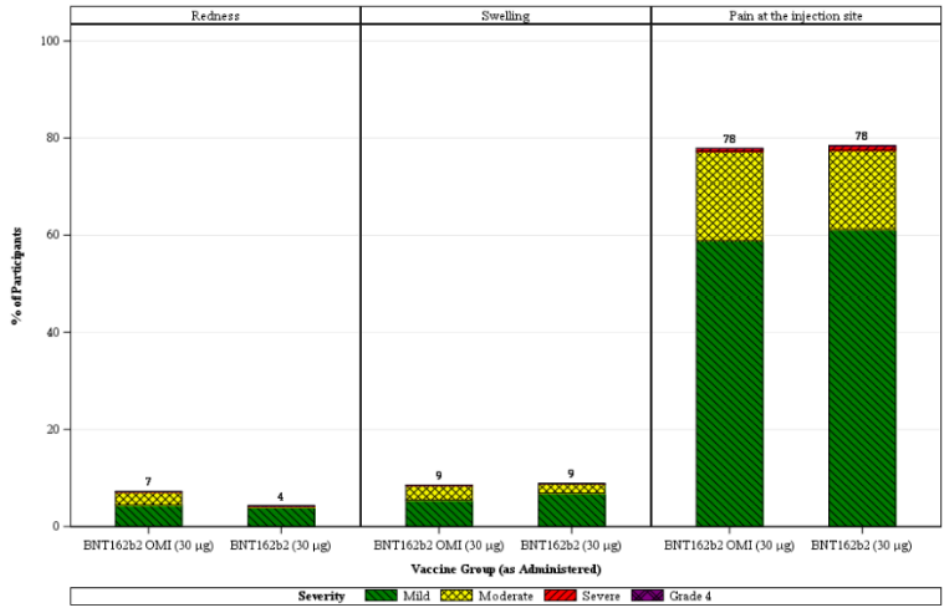
PFIZER CONFIDENTIAL SDTM Creation: 11APR2022 (01:32) Source Data: adsl Table Generation: 03JUN2022 (15:34)
(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File:

5.3.2 Reactogenicity

Local reactions

The reported local reactions are illustrated in figure 4 below. Most events were mild or moderate in severity and no grade 4 local reactions were reported. For both groups, the median onset for all local reactions was 1 to 2 days, and all events resolved within a median duration of 1 to 2 days after onset.

Figure 4. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After First Study Vaccination – Cohort 2 – Safety Population

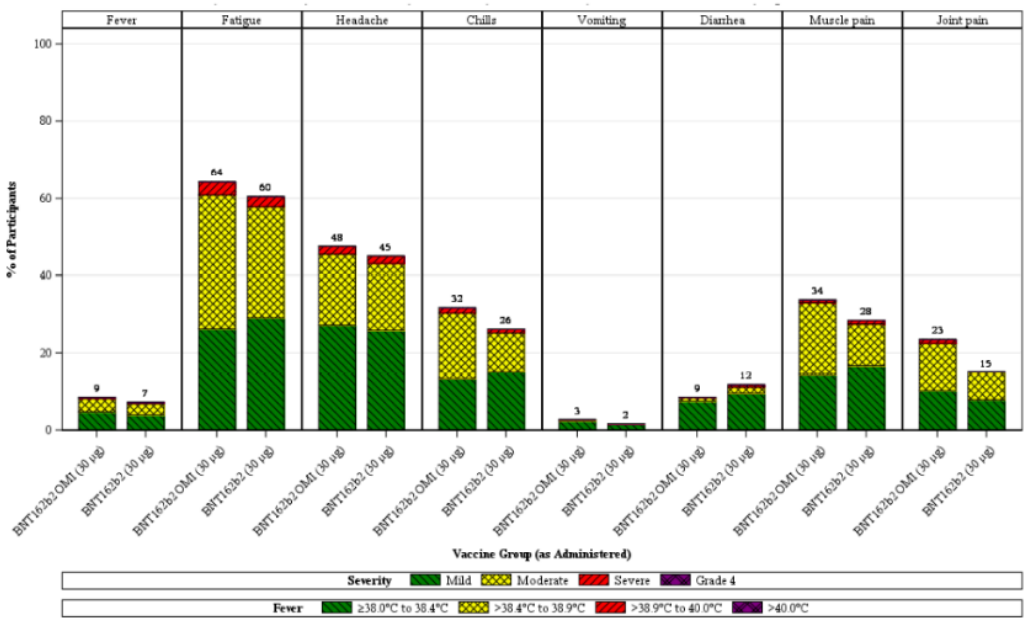


Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 08APR2022 (22:11) Source Data: adfacevd Table Generation: 18MAY2022 (02:10)
(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File: /nda2_ubd/C4591031_D/adce_f001_lr_max_c2

Systemic reactions

The reported systemic reactions are illustrated in figure 5 below. In both groups, there was 1 participant (0.3%) with fever >38.9 °C to 40.0 °C; there were no participants in either group with fever >40.0 °C. For both groups, the median onset for most systemic events was 1 to 2 days, and all events resolved within a median duration of 1 to 2 days after onset.

Figure 5. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After First Study Vaccination – Cohort 2 – Safety Population



Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 08APR2022 (22:11) Source Data: adfacevd Table Generation: 18MAY2022 (02:10)
(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File: /nda2_ubd/C4591031_D/adce_f001_se

Across the BA.1 30µg OMI and Original 30µg vaccine groups, the frequencies of the most commonly reported systemic events of fatigue and headache were ≤63.0% and ≤39.0%, respectively, for male

and ≤70.5% and ≤62.3%, respectively, female participants, respectively. There were no differences in severity between sex in terms of reported local reactions.

5.3.3 Adverse Events

Participants reporting AEs from first study (Dose 4) vaccination to 1 month after Dose 4 are described in Table 19 below.

Table 51. Number (%) of Participants Reporting at Least 1 Adverse Event From First Study Vaccination Through 1 Month After First Study Vaccination –Cohort 2 – Safety Population

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 OMI (30 µg) (N[a]=315) n[b] (%)	BNT162b2 (30 µg) (N[a]=325) n[b] (%)
Any adverse event	18 (5.7)	12 (3.7)
Related[c]	10 (3.2)	5 (1.5)
Severe	4 (1.3)	2 (0.6)
Life-threatening	0	0
Any serious adverse event	1 (0.3)	1 (0.3)
Related[c]	0	0
Severe	0	1 (0.3)
Life-threatening	0	0
Any nonserious adverse event	17 (5.4)	12 (3.7)
Related[c]	10 (3.2)	5 (1.5)
Severe	4 (1.3)	1 (0.3)
Life-threatening	0	0
Any adverse event leading to withdrawal	0	0
Related[c]	0	0
Severe	0	0
Life-threatening	0	0
Death	0	0

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any event," n = number of participants reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to study intervention.
PFIZER CONFIDENTIAL SDTM Creation: 08APR2022 (22:11) Source Data: adae Table Generation: 18MAY2022 (01:54)
(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File: ./nda2_ubd/C4591031_D/adae_s091_all_saf

The frequency of any AE after Dose 4 dose administration was ≤6.7% in male participants and ≤4.6% in female participants across vaccine groups. Related AEs were reported by ≤3.7% of male participants and ≤2.6% of female participants (with numerical differences between vaccine groups driven by reactogenicity events in these subgroups).

Most AEs reported during this period reflect reactogenicity events (ie, fatigue, chills, myalgia, pyrexia, headache, injection site pain), which accounted for the majority of severe AEs. The SOCs in which the reactogenicity terms are included had the following overall AE frequencies in the BA.1 30µg group versus Original 30µg group:

- general disorders and administration site conditions: 9 (2.9%) vs 0

- musculoskeletal and connective tissue disorders: 5 (1.6%) vs 2 (0.6%)
- nervous system disorders: 4 (1.3%) vs 1 (0.3%)
- gastrointestinal disorders: 0 vs 2 (0.6%)

Table 52. Number (%) of Participants Reporting at Least 1 Adverse Event From First Study Vaccination Through 1 Month After First Study Vaccination, by System Organ Class and Preferred Term –Cohort 2 – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 OMI (30 µg) (N[a]=315)		BNT162b2 (30 µg) (N[a]=325)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	18 (5.7)	(3.4, 8.9)	12 (3.7)	(1.9, 6.4)
Blood and lymphatic system disorders	1 (0.3)	(0.0, 1.8)	3 (0.9)	(0.2, 2.7)
Lymphadenopathy	1 (0.3)	(0.0, 1.8)	3 (0.9)	(0.2, 2.7)
Cardiac disorders	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.7)
Palpitations	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Tachycardia	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Gastrointestinal disorders	0	(0.0, 1.2)	2 (0.6)	(0.1, 2.2)
Diarrhoea	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Mouth ulceration	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
General disorders and administration site conditions	9 (2.9)	(1.3, 5.4)	0	(0.0, 1.1)
Fatigue	5 (1.6)	(0.5, 3.7)	0	(0.0, 1.1)
Chills	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.1)
Chest pain	2 (0.6)	(0.1, 2.3)	0	(0.0, 1.1)
Pyrexia	2 (0.6)	(0.1, 2.3)	0	(0.0, 1.1)
Axillary pain	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Injection site pain	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Infections and infestations	0	(0.0, 1.2)	3 (0.9)	(0.2, 2.7)
Herpes zoster	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Impetigo	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Otitis media acute	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Sinusitis	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Injury, poisoning and procedural complications	2 (0.6)	(0.1, 2.3)	0	(0.0, 1.1)
Concussion	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Road traffic accident	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Skin laceration	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Metabolism and nutrition disorders	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Fluid retention	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)

Musculoskeletal and connective tissue disorders	5 (1.6)	(0.5, 3.7)	2 (0.6)	(0.1, 2.2)
Arthralgia	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.7)
Myalgia	2 (0.6)	(0.1, 2.3)	0	(0.0, 1.1)
Joint swelling	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Nuchal rigidity	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Rotator cuff syndrome	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Soft tissue swelling	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Nervous system disorders	4 (1.3)	(0.3, 3.2)	1 (0.3)	(0.0, 1.7)
Dizziness	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.7)
Headache	2 (0.6)	(0.1, 2.3)	0	(0.0, 1.1)
Migraine	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Psychiatric disorders	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Anxiety	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.7)
Cough	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Sneezing	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Skin and subcutaneous tissue disorders	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Night sweats	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)

Note: MedDRA (v24.1) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 08APR2022 (22:11) Source Data: adae Table Generation: 18MAY2022 (01:54)
(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File:

Related AEs

Table 53. Number (%) of Participants Reporting at Least 1 Related Adverse Event From First Study Vaccination Through 1 Month After First Study Vaccination, by System Organ Class and Preferred Term –Cohort 2 – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 OMI (30 µg) (N[a]=315)		BNT162b2 (30 µg) (N[a]=325)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	10 (3.2)	(1.5, 5.8)	5 (1.5)	(0.5, 3.6)
Blood and lymphatic system disorders	1 (0.3)	(0.0, 1.8)	3 (0.9)	(0.2, 2.7)
Lymphadenopathy	1 (0.3)	(0.0, 1.8)	3 (0.9)	(0.2, 2.7)
Gastrointestinal disorders	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Diarrhoea	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
General disorders and administration site conditions	9 (2.9)	(1.3, 5.4)	0	(0.0, 1.1)
Fatigue	5 (1.6)	(0.5, 3.7)	0	(0.0, 1.1)
Chills	3 (1.0)	(0.2, 2.8)	0	(0.0, 1.1)
Chest pain	2 (0.6)	(0.1, 2.3)	0	(0.0, 1.1)

Pyrexia	2 (0.6)	(0.1, 2.3)	0	(0.0, 1.1)
Axillary pain	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Injection site pain	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Musculoskeletal and connective tissue disorders	3 (1.0)	(0.2, 2.8)	1 (0.3)	(0.0, 1.7)
Arthralgia	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.7)
Myalgia	2 (0.6)	(0.1, 2.3)	0	(0.0, 1.1)
Nuchal rigidity	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Nervous system disorders	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.7)
Dizziness	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.7)
Headache	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)
Cough	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.1)

Note: MedDRA (v24.1) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 08APR2022 (22:11) Source Data: adae Table Generation: 18MAY2022 (01:54)
(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 8APR2022) Output File:

Immediate AEs

No immediate AEs (occurring within 30 minutes post-vaccination) were reported after first study (Dose 4) vaccination for either vaccine groups.

Severe and Life-Threatening AEs

From first study (Dose 4) vaccination to 1 month after Dose 4, the frequency of severe AEs was low for the BA.1 30µg (4 participants [1.3%]) and the Original 30µg groups (2 participants [0.6%]). In the BA.1 30µg group, all were severe reactogenicity events: fatigue, chills, arthralgia, and headache. Severe AEs reported in the Original 30µg group were fluid retention (SAE, assessed as not related) and diarrhoea. No life-threatening (ie, Grade 4) AEs were reported after Dose 4 in either vaccine group.

Serious AEs

From first study (Dose 4) vaccination to 1 month after Dose 4, 2 participants, 1 in each group, reported 1 SAE each, both of which were assessed as not related:

- In the BA.1 30µg group, there was 1 event of migraine (unrelated) reported 22 days after Dose 4 that was ongoing as of the data cut-off date.
- In the Original 30µg group, there was 1 event of fluid retention (unrelated) reported 25 days after Dose 4 and resolved within 6 days.

Discontinuation from Study due to AEs

No participants in the study were withdrawn due to AEs from first study (Dose 4) vaccination to the data cut-off date of 11 March 2022.

Other Significant AEs

No cases of anaphylaxis, hypersensitivity, myocarditis, pericarditis, appendicitis, Bell's Palsy, or rash were reported in either group in C4591031 Substudy D from first study (Dose 4) vaccination to up to 1-month post-Dose 4 or to the data cut-off date. Lymphadenopathy is considered an adverse reaction to Original 30µg, and events are discussed below. Additional AEs of clinical interest, including those on

the CDC AESI list, were evaluated based on sponsor agent safety data review. These AEs were identified from the C4591031 study database as of the data cut-off date. From the analysis of reported AEs, there were no additional safety concerns. Notable pertinent negatives (ie, no cases reported in this population as of the data cut-off for this report) with regard to the CDC list of AESIs included (but were not limited to): arthritis, thrombocytopenic events, thromboembolic or intravascular coagulation events, autoimmune or demyelination events, myocarditis, pericarditis, meningitis, encephalitis, optic neuritis, peripheral neuropathy, vasculitis, Kawasaki disease, MIS, or acute respiratory distress syndrome. AESIs of chest pain and herpes zoster are discussed below.

Lymphadenopathy
From Dose 4 to the data cutoff date, lymphadenopathy was reported in 1 participant (0.3%) and 3 participants (0.9%) in the BA.1 30µg and Original 30µg groups, respectively. All 4 events were considered by the investigator as related to study intervention and occurred in the older (31 to 55 years) age group. Cases of lymphadenopathy were mild to moderate, occurred within 2 to 3 days after Dose 4 dose administration, were located in the axillae (predominantly) or cervical nodes, and recovered/resolved within 3 to 8 days (with sequalae for the participant in the BNT162b2 group). Additionally, 1 participant (0.3%) in the BA.1 30µg group reported axillary pain (Grade 1, assessed as related). The event occurred 3 days after Dose 4 and was resolved within 6 days.

Chest Pain
In the BA.1 30µg group, there were 2 events of chest pain, both Grade 1 and assessed as related.

- In a 25 – 34-year-old female, chest pain was reported 4 days after Dose 4 and was resolved within 3 hours with no other symptoms. The investigator considered the event as stress related and did not think it met criteria for cardiac illness; no further investigations were performed. The physician noted a temporal relationship (stress relating to 'anxiety' from recent receipt of the vaccine) and the event was designated as related to the investigational product. The participant had no other reported AEs.
- In a 35 – 44 year- old male, chest pain was reported 2 days after Dose 4 and was resolved within 10 days. Pain was constant for the first 2 days and decreased to a few minutes a day afterward. The participant had no shortness of breath or palpitations. The event was assessed as related to investigational product. At a cardiac illness visit 5 days after the event onset, the participant had no elevation in troponin, mean heart rate was 78 beats/minute, ECG normal, and echocardiography was normal. The participant had no other reported AEs.

Herpes Zoster

In 1 participant in the Original 30µg group, an AE of herpes zoster (mild, resolved, assessed as unrelated) was reported 1 day after Dose 4. No other AEs were reported for the participant.

C4591031 Substudy D summary

Reactogenicity Profile
Overall, the reactogenicity profile (local reactions, systemic events) within 7 days after BA.1 30µg and Original 30µg administered as a fourth dose was similar to that previously observed after a third dose of Original 30µg. Analyses by age, sex, race, ethnicity, and baseline SARS-CoV-2 status suggested no meaningful differences across subgroups or between vaccine groups for the overall patterns of local reactions or systemic events, although due to limited numbers in some subgroups, the subgroup analyses should be interpreted with caution.

- Local reactions were mostly mild to moderate, with the majority of events arising within the first 1 to 2 days after dosing and were short-lived. The most common prompted local reaction

was pain at the injection site (≤78.4%) in both groups. Few severe (≤1.0%) and no Grade 4 local reactions were reported.

- Systemic events were mostly mild to moderate, with the majority of events arising within the first 1 to 2 days after dosing and were short-lived. The most common prompted systemic events were fatigue (≤64.3%) and headache (≤47.6%) in both groups. Few severe (≤3.4%) and no Grade 4 systemic events were reported.

Adverse Event Profile
The AE profiles after Dose 4 of Original 30µg or BA.1 30µg were similar, reflected mostly reactogenicity events, and did not suggest any clinically important short-term safety concerns. Subgroup analyses did not suggest any specific safety concerns with regard to age, sex, race, ethnicity, or baseline SARS-CoV-2 status. From Dose 4 to 1-month post-Dose 4, a similar proportion of participants in the BA.1 30µg group (5.7%) reported any AE compared with the Original 30µg group (3.7%). This was driven primarily by any AEs considered by the investigator as related to study intervention, reported by 3.2% of participants in the BA.1 30µg group and 1.5% of participants in the Original 30µg group. Any severe or serious AEs were reported across the BA.1 30µg and Original 30µg groups by ≤1.3% and ≤0.3%, respectively.
The proportion of participants reporting any AE after Dose 4 to the data cut-off date of 11 March 2022, which represents up to at least 1-month post-Dose 4 follow-up, was similar in the BA.1 30µg (5.7%) and Original 30µg (3.7%) groups. No additional AEs were reported between 1 month after Dose 4 to the data cut-off date.
After Dose 4, there were few AEs of clinical interest reported in both BA.1 30µg and Original 30µg groups. Lymphadenopathy is considered an adverse reaction to Original 30µg and was observed after Dose 4 in both BA.1 30µg (n=1) and Original 30µg (n=3) groups. No cases of anaphylaxis, hypersensitivity, myocarditis/pericarditis, appendicitis, Bell's Palsy, or rash were reported in either group over the course of at least 1 month of follow-up after Dose 4 in individuals 18 to 55 years of age.

5.4 Discussion

Evidence base for the safety of Original/Omicron BA.1 15/15ug

The MAH has provided 1-month interim data from study C4591031 *substudy E* in which the already authorized monovalent "Original 30µg" was compared with five different vaccines of different composition: monovalent "Original" 60µg, monovalent Omicron BA.1 "BA.1" 30µg, monovalent Omicron BA.1 "BA.1" 60µg and two bivalent combinations of Original/BA.1 (15/15µg and 30/30µg).

Only data for subjects aged >55 years of age have been presented by the company. This study included 1841 subjects, most of which (89%) had a follow-up time of ≥1 month to <2 months after vaccination. 305 subjects received the Original/BA.1 15/15 µg vaccine.

All doses were administered as a fourth dose, and all subjects had already received 3 doses of Original 30µg.

Data from C4591031 *substudy D* has also been provided. In this dataset 640 subjects aged 18-55 years were randomized to receive either the monovalent BA.1 30 µg (n=315) or the authorized Original 30 µg (n=325) as a fourth dose. All 640 subjects received one dose of either vaccine.

Thus, reactogenicity and safety data are available for the bivalent Original/BA.1 15/15 µg vaccine in subjects aged 55 and higher. In subjects below this age, data are only available for a monovalent BA.1 vaccine variant at 30ug.

In both *substudy D and E*, reactogenicity (systemic and local events) and use of antipyretic/pain medication was recorded for 7 days after administration of each dose by using an e-diary. AEs were collected for 1 month and SAEs for 6 months after dosing. Acute reactions were recorded as immediate if they occurred within 30 min after administration of the vaccine.

Most of the included subjects in both *substudy D and E* were white. The studies were executed in the US and the distribution between gender was balanced. It is noted that 71-73% of the subjects were overweight or obese.

In substudy E, all participants, except one subject in the Original/BA.1 15/15µg group, received their booster dose at least 5 months after their last vaccination (median time 6,3 months, range 5-13 months.

In *substudy E* the median age was 67 years. In *substudy D* all subjects received their fourth dose at a median time of 4 months after their last vaccination (range 3,3-6,8 months) and the median age was 43 years, and only 13% (n=84) of the entire study population were 18-30 years old.

Reactogenicity

Pain at injection site was the most frequently reported local reaction in all study groups in *substudy E*. (58% Original/BA.1 15/15µg; 60% Original 30µg; 68% Original/BA.1 30/30µg).

Most of the local reactions were mild to moderate in severity, no grade 4 reaction were reported.

The median time to onset for the local reactions was 2 days and all events resolved within a median duration of 1-2 days after onset.

In *substudy D*, pain at the injection site was the most common local reaction in both BA.1 30µg and Original 30µg (78% each).

Most of the local reactions were mild or moderate in severity and no Grade 4 local reactions were reported.

For both groups, the median onset for all local reactions was 1 to 2 days, and all events resolved within a median duration of 1 to 2 days after onset.

In *substudy E*, the most frequently reported systemic reactions were fatigue (49% Original/BA.1 15/15 µg; 45% Original 30 µg; 57% Original/BA.1 30/30µg); headache (34% Original/BA.1 15/15µg; 27% Original 30 µg; 37% Original/BA.1 30/30µg); muscle pain (22% Original/BA.1 15/15µg; 20% Original 30µg; 27% Original/BA.1 30/30µg), chills (13% Original/BA.1 15/15 µg; 16% Original 30µg; 24% Original/BA.1 30/30µg), joint pain (11% Original/BA.1 15/15 µg; 9% Original 30µg; 19% Original/BA.1 30/30µg) and fever (5% Original/BA.1 15/15µg; 4% Original 30µg; 8% Original/BA.1 30/30µg).

Four events of fever >38,9-40°C were reported in the group that received Original/BA.1 15/15µg vaccine, whereas none in the Original 30µg reported fever >38,9°C. The only event of fever >40,0°C was reported by a subject that received BA.1 60µg; in that group four events of fever >38,9-40°C were also reported.

Most systemic events were mild or moderate in severity.

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

It was noted that the group receiving BA.1 60 µg reported a slightly higher frequency and severity of systemic reactions compared to the other study arms. This is indicative of the importance of the mRNA dose for the reactogenicity profile, and indicative that the extrapolation of the reactogenicity of a

higher dose from older to younger subjects might not be appropriate. Moreover, there was a general tendency for numerically higher rates of systemic reactions when the vaccine included Omicron BA.1.

In the *substudy D*, fatigue was the most reported systemic reaction (64% BA.1 30µg; 60% Original 30 µg), followed by headache (48% BA.1 30µg; 45% Original 30 µg), muscle pain (34% BA.1 30 µg; 28% Original 30 µg). Fever events were reported 9% BA.1 30 µg; 6% Original 30µg.

Most of the events were mild or moderate in severity and no Grade 4 systemic events were reported.

For both groups, the median onset for most systemic events was 1 to 2 days, and all events resolved within a median duration of 1 to 2 days after onset.

In *substudy E*, antipyretic or pain medication were used at similar frequency for the subjects that received Original/BA.1 15/15 µg (29%) as for the subject that received Original 30 µg (27%).

In summary, the frequency of local reactions was slightly higher among the younger subjects included in *substudy D* compared with the older adults included in *substudy E*. This would be anticipated, as reactogenicity is generally higher in younger compared to older subjects. Yet higher rates are anticipated in adolescents aged 12-18, as is the case for the Original 30µg vaccine. Moreover, similar to *substudy E*, the rate of systemic reactions tended to be numerically higher with the Omicron BA.1 vaccine construct compared to the original.

Thus, across the two trials, there is a tendency for numerically slightly higher frequencies of reactogenicity-related events with BA.1 containing vaccines. However, these differences are marginal and not deemed clinically meaningful, and do not preclude the extrapolation of safety from the >55 to younger adults, as described below.

Overall adverse events

AEs in *substudy E* were reported for the time period up to 1 month after dosing and up to cutoff date (16MAY2022) which represents a median follow-up of at least 1.7 months after study vaccination.

The rate for any AEs up to the cutoff date in *Substudy E* was roughly similar across treatment arms (range: 3.9% (BA.1 60µg) - 10.4% (Original/BA.1 30/30 µg)).

Severe AEs were uncommonly reported across study arms.

No additional safety concern was observed regarding AEs in *Substudy D*. The number of any reported AE was overall low (5,7%, BA.1 30µg; 3,7%, Original 30µg).

Though slightly higher rates of adverse events were noted among females, there were no meaningful differences in reactogenicity or other adverse events between subgroups based on race, ethnicity or evidence of prior SARS-Cov-2 infection.

There were no cases reported of myocarditis/pericarditis, Bell's palsy (or facial paralysis/paresis), or vaccine-related anaphylaxis, in either study.

There were no deaths in the studies and no new safety concerns compared to what is known of Comirnaty Original, were identified.

Altogether, no clinically relevant differences in the AE profile were seen between study arms for the time period up to 1 month compared to time interval up to cutoff. However, the size of the safety database for BA.1 containing variant vaccines is not large enough to characterise the frequency of rare adverse events. Therefore, it is not known whether the risk of myocarditis is similar for the original vaccine, and the Original/BA.1 15/15µg variant vaccine. This, however, would require very large studies to characterise, which is only feasible in a post-authorisation setting.

Conclusion on clinical safety

While systemic reactogenicity events may be somewhat more common when an Omicron component is included in the booster, the reactogenicity profile of a booster dose with bivalent vaccine Original/BA.1 15/15µg does not appear meaningfully different from that reported earlier for Original 30µg primary vaccine series and booster. This would be anticipated, given that the products differ only with respect to the spike protein sequence of the Omicron BA.1 component. Whether rare adverse events based on molecular mimicry differ, is unknown.

Safety data for Original/BA.1 15/15µg is at this stage only available in subjects aged >55 years. However, based on (a) a similar total dose of mRNA, (b) no relevant differences in reactogenicity between Original and Original/BA.1 in those aged above 55, and (c) no relevant differences in reactogenicity between Original and BA.1 in those below 55, the inference may be drawn that reactogenicity will be acceptable also in adults below 55. Consequently, a substantially different safety profile in adolescents or younger adults, compared to the available Original 30µg, is considered sufficiently unlikely.

There are no safety data for the use of Original/Omicron BA.1 15/15 as a third dose in total, as a fifth dose in total, or after a primary series with another COVID-19 vaccine. Moreover, there are no safety data for a repeat booster with Original/Omicron BA.1 15/15. However, there are no reasons to believe that the safety profile would differ substantially in any of these scenarios as this was not seen for the original vaccine.

Immunogenicity and safety of the Original/BA.1 15/15µg vaccine in subjects aged 18-55 is currently being assessed in an ongoing study. Data from this study will be reported as a post authorisation commitment.

No data has been presented on BA.1-variant vaccine in pregnancy. However, the total mRNA dose is the same as for Original vaccine, and reactogenicity is similar. Moreover, as noted, the only difference between products lies in the spike protein sequence. Therefore, a conclusion of acceptable safety in pregnancy and breast-feeding as well as the safety profile in general is drawn by the CHMP for the variant vaccine.

6. Risk management plan

The MAH submitted an updated RMP **version 6.0** (date of final sign off 18 July 2022) with this application. After assessment comments, the MAH updated the RMP to **version 6.1** (date of final sign off 24 August 2022).

- The (main) proposed RMP changes were the following (note the updated sections only are reflected in the table below):

Part I PRODUCT OVERVIEW	Addition of Comirnaty Original/Omicron BA.1 (15/15 mcg) data according to the updated SmPC
Part II SAFETY SPECIFICATION	
Part II Module SI Epidemiology of the Indication(s) and Target Populations	Minor update
Part II Module SIII Clinical Trial Exposure	Addition of text and CT relevant exposure tables from C4591031 Substudy E and C4591031 Substudy D as supportive data

	All the exposure tables not in scope for Comirnaty Original/Omicron BA.1 (15/15 mcg) submission are removed from the module and included in Annex 7
Part II Module SIV Populations Not Studied in Clinical Trials	Updated with relevant exposure from C4591031 Substudy E and Substudy D
Part II Module SV Post-Authorisation Experience	Updated with new DLP 15 April 2022
Part II Module SVII Identified and Potential Risks	Updated to remove the important identified risk of anaphylaxis Addition of data related to booster dose by age group for the important risks myocarditis and pericarditis and VAED/VAERD and DLP revised as per table above
Part II Module SVIII Summary of the Safety Concerns	Updated to remove the important identified risk of anaphylaxis as previously agreed with EMA
Part III PHARMACOVIGILANCE PLAN (INCL POST AUTHORISATION SAFETY STUDIES)	
III.1 Routine Pharmacovigilance Activities	Updated to remove reference to the DCA for anaphylaxis from the document because Anaphylaxis is removed as an important identified risk Updated to remove reference to summary safety reports as per the final EMA/PRAC assessment (PAM-MEA-002.13) Updated to add Comirnaty Original/Omicron BA.1 (15/15 mcg) formulation in the vial differentiation description
III.2 Additional Pharmacovigilance Activities	Updated to remove reference to anaphylaxis
III.3 Summary Table of Additional Pharmacovigilance Activities	Milestone updated for studies: C4591007, C4591009, C4591036 and BNT 162-01 Cohort 13
PART VI SUMMARY OF THE RISK MANAGEMENT PLAN	
I The Medicine and What It Is Used For	Updated to include Comirnaty Original/Omicron BA.1 (15/15 mcg)
II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks	Updated based on the changes made in PART III and PART V
PART VII ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 2: Studies/milestones updated Annex 4: DCA for anaphylaxis is removed Annex 7: CT exposure tables (not in scope for this Comirnaty Original/Omicron BA.1 15/15 mcg

	submission) moved to this annex Annex 8: Changes to reflect the updates

- Note that **relevant parts** only (e.g. Summary of the safety concerns) including **relevant parts from the RMP covering proposed changes** are reproduced below.

PART II SAFETY SPECIFICATION

Module SIII Clinical trial exposure

This module of the RMP has been updated with the *Evaluation of additional boosting dose(s)* providing new clinical data in approximately 1840 participants >55 years of age from ongoing C4591031 *Substudy E* (BNT162b2-experienced participants), including safety and immunogenicity data up to 1 month after receipt of a single dose (Dose 4) of BNT162b2 (30 or 60µg), monovalent BNT162b2 OMI (30 or 60µg), or bivalent BNT162b2 + BNT162b2 OMI (30 or 60µg).

In addition, clinical data from approximately 640 participants ≥18 to ≤55 years of age from ongoing Study C4591031, phase 3 Substudy D (Cohort 2: BNT162b2-experienced participants), including safety and immunogenicity to 1 month after receipt of an additional booster (fourth) dose of an Omicron variant specific vaccine, BNT162b2 OMI 30 µg are provided.

Module SVII Identified and potential risks

This module of the RMP has been updated to *remove* Anaphylaxis as an important identified risk in the list of safety concerns (EMEA/H/C/005735/II/0087, issued 10 March 2022) because anaphylaxis is a known risk of vaccines that is understood by HCPs who administer vaccines and patients and does not considerably impact the benefit/risk profile of the vaccine. Product labelling and standards of medical care during the vaccination procedure provide adequate risk mitigation.

Module SVIII Summary of the safety concerns

Anaphylaxis has been removed as an important identified risk.

Table . Summary of 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

PRAC and CHMP consider the safety concerns listed above are appropriate.

PART III PHARMACOVIGILANCE PLAN (INCL POST AUTHORISATION SAFETY STUDIES)

Routine Pharmacovigilance Activities

This section has been updated to remove reference to summary safety reports as per the final EMA/PRAC assessment (PAM-MEA-002.13 issued 08 June 2022).

In addition, subsection Potential Medication errors has been updated to add Comirnaty Original/Omicron BA.1 (15/15 mcg) formulation in the vial differentiation description.

Large scale public health approaches for vaccination may represent changes to standard vaccine treatment process with the use of various formulations to different healthcare settings based on age (ie. less than 12 years and above 12 years of age). This represents the likelihood of the purple (DILUTE BEFORE USE) and grey (DO NOT DILUTE) vials co-existing in the same setting. These potential medication errors are mitigated through the information in the label (colour of label boarder, product name on the label) and available educational materials for healthcare providers.

Note that a meeting between the EMA and the MAH has been taken place in June 2022 to clarify the colour code system of the vials. The MAH's strategy is based on the use of different cap colours to distinguish the different authorised presentations for 3 different age groups (grey flip-off caps >12 years and ready to use formulation, orange flip-off caps 5 to 11 years, brown flip-off caps intended for the 6 months to 4 years). Hence, according to the MAH the introduction of new cap colours for each variant-adapted vaccine in addition to the use of colours to support age groups would create further complexity in the colour codes used and may potentially increase the risk of confusion with the different dose levels / formulations resulting in an increase in medication errors that have a higher impact on safety (wrong dose / administration of undiluted concentrate).

Apart from manufacturing issues and the fact that the availability of cap colours is limited, the MAH claims that any change on the cap colour will delay the launch by 7 months, as standard colours (off the shelf) are limited in number by the range offered by the manufacturers. Extraordinary colours (not off the shelf) would offer a broader range but only under extended lead times. Also the availability of caps is limited. Due to the high demand of caps and the impaired global supply chains, the availability of caps independent on the colour is limited. The capacity of cap production has the potential to limit vaccine production. In case of a non-standard colour, the continuous supply and initial ramp up capacity of those caps would increase the risk of supply constraints.

To reduce the potential of Medication errors, various educational resources (e.g. poster, dosing card, medical information call centers, traceability and vaccination reminder card) to inform HCPs on the proper preparation and differentiation will be available.

When considering the risk of medication errors due to the mix-up of different vials, from a safety perspective the most relevant medication error would be the administration of a presentation for adults to children or the presentation for older children administered to younger children, as such medication errors would lead to overdose. The MAH’s strategy to distinguish cap colours for different age groups would mitigate this risk of medication error. Medication errors due to mix-up between Comirnaty Original (monovalent) and Comirnaty bivalent vaccines – same cap colour for one age group – are not mitigated with this strategy. However, considering the safety profiles of the monovalent and bivalent vaccine appears to be comparable, a safety concern is considered limited. Furthermore, it is noted that introduction of different colour flip-off caps would take about 7 months, by when HCPs would presumably be familiar with handling different presentation with same colour flip-off caps.

It is acknowledged that introduction of new cap colours for each variant-adapted vaccine in addition to the use of colours to support age groups would result in at least 3 additional colours for all dose levels for an omicron-adapted vaccine. The MAH argues that this would create further complexity in the

colour codes used and may potentially increase the risk of confusion with the different dose levels / formulations resulting in an increase in medication errors that have a higher impact on safety (wrong dose / administration of undiluted concentrate).

However, expert input from clinical practice raised concerns about the same colour flip off for 'Comirnaty original' and the new bivalent vaccine. As it cannot be ruled out that in future a new/further variant vaccine is developed and introduced, the MAH is requested to prepare for such scenario (also regarding flip off caps to avoid that time needed to arrange for other colour caps would be a blocking issue). While respecting the MAH's current colour coding strategy, an option could be to use light and dark colour flip off caps for existing and new vaccines.

Various educational resources (e.g. poster, dosing card, medical information call centers, traceability and vaccination reminder card) are already in place and will be updated with the introduction of this modified vaccine. These are considered routine risk minimization measures and considered sufficient at this stage.

The MAH confirmed, further to the launch of the modified vaccines, their commitment to carefully monitor medication errors and inform the authorities immediately in case of any unexpected findings or trends.

Additional Pharmacovigilance Activities

This section has been updated with revised milestones (*Italics*) for the following safety studies (the full table with all additional PV studies is included in the RMP):

Study number and title	Country	Interventional/ non-interventional/ low-interventional	Milestone update and rationale for milestone update
C4591007, a phase 1, open-label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children and young adults	Global *Ongoing*	Interventional	Final CSR submission: ~~31~~ *03* ~~July~~ *Dec* 2024 *The new timeline (endorsed by EMA on 24 March 2022) for availability of the final report is due to the amendments introduced over time to the study design*
C4591009, a non-interventional post approval safety study Pfizer-BioNTech COVID-19 vaccine in the United States	US *Ongoing*	Non-interventional	Protocol submission: 31-Aug- 2021 Protocol amendment submission ~~(booster dose)~~: ~~31 Dec 2021~~ *11-Jul-2022* Monitoring report *1* submission: 31 Oct 2022 *Monitoring report 2 submission: 31 Oct 2024* Interim Analysis submission: 31 Oct 2023 Final CSR submission: 31 ~~Oct~~ *Mar* ~~2025~~ *2026* *FDA requested a protocol amendment to incorporate analyses in the 6 months- 4 years group. As part of the amendment, there were changes to the end of data collection and final study report milestone dates*
C4591036 (former Pediatric Heart Network), low-interventional cohort study of myocarditis/ pericarditis associated with COMIRNATY in persons less than 21 years of age	US/CA *Planned*	~~Non~~ *Low*-interventional	Protocol submission: 30 Nov 2021 Final CSR submission: 31 ~~Oct~~ *Dec* ~~2025~~ *2029* *The date of the final report has been extended based on the FDA's requirement to increase the sample size for Cohort 1 to 300 participants; this was also endorsed by EMA on 16 May 2022*

Study number and title	Country	Interventional/ non-interventional/ low-interventional	Milestone update and rationale for milestone update
BNT 162-01 Cohort 13, Immunogenicity of Pfizer BioNTech COVID 19 vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses.	EU *Ongoing*	Interventional	IA submission: 30 Sep 2021 Final CSR submission: 31 ~~Dec~~ *Oct* ~~2022~~ *2023* *Protocol amendment 6.0 implemented three additional cohorts which led to increase of study duration and postponing of final study report submission (endorsed by EMA on 16 May 2022)*

Considering section *III.1 Routine Pharmacovigilance Activities* of the RMP, it was suggested to rephrase the wording *educational materials* in subsections *Potential Medication Errors* and *Cold-chain Handling and Storage* to avoid confusion. Note there are several resources (e.g. traceability, medical information call centers available for HCP etc.) and reference materials (e.g. poster with instruction for vaccine storage, brochures for safe handling of the vaccine, vaccination reminder card etc.) in place. However, these are all considered routine PV activities. As requested, in RMP v 6.1, the wording *educational materials* has been rephrased into *resources and referenced materials* in line with Annex 7 of the RMP.

Considering the *Additional Pharmacovigilance Activities*, the modified vaccine Original/Omicron BA.1 did not seem to be addressed in the ongoing PASSs included in the RMP v 6.0. However, the MAH will assess the non-interventional studies C4591012 (US), C4591021 (EU), and C4591036 (US/CA former Paediatric Heart Network [PHN]) for the feasibility of studying the bivalent Omicron-modified vaccine. The MAH notes that feasibility is dependent on the ability to uniquely identify the bivalent vaccine as the booster dose administered. Additionally, the MAH will explore the feasibility of a new stand-alone study in the general US population and in sub-cohorts of interest, who have received the bivalent Omicron-modified vaccine. Due to measures implemented by the MAH (e.g. differences in naming, labelling), the bivalent vaccine will be uniquely identified. In view of the limited clinical data available for the bivalent vaccine compared to the initial monovalent vaccine, it is important that further safety data on the bivalent vaccine is collected in the post-marketing setting and the modified vaccine needs to be addressed in all PASSs. The MAH was requested to include the current bivalent vaccine as well as future modified vaccines in all ongoing PASSs; the MAH committed to submit the PASS protocol amendments as soon as possible; further details and discussion will be included in an updated RMP submitted at the earliest regulatory opportunity.

Overall conclusions on the PhV Plan

The proposed *updated* post-authorisation PhV development plan (per RMP v.6.1) is considered sufficient to identify and characterise the risks of the product.

Overall conclusion on the RMP

☒ The changes to the RMP are acceptable. RMP version 6.1 is considered approved with this variation. Further discussions on the post-marketing pharmacovigilance planning adapted to the new formulation(s) will continue in the framework of upcoming variation(s).

7. Changes to the Product Information

As a result of this variation, the SmPC and the Package Leaflet (PL) have been updated.

Please refer to the attached PI which includes all proposed changes to the Product Information.

Quick Response (QR) code

The updated content of the QR code has been assessed in EMEA/H/C/005735/N/0132 and in an updated Art.61(3) Comirnaty: QR-Code website - proposed updates to reflect new presentations.

The main proposed changes are clear references to the SmPC/PL instead of repeating information separately on the web page. Furthermore, clear tables stating each and respective presentation are proposed. These tables should be complemented with complete name for easier identification, which is also in line with the ongoing discussion on the colour of the flip off cap, where the prominence of the

product name should be the focus for distinguishing products, rather than trusting the cap colour only.

The principles for the web page are endorsed, however, concerning future presentations, publishing of these web pages should be timed.

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) document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 vaccines for EU citizens within the existing legal framework

Labelling exemptions

Outer and immediate labelling (from start of supply to end 2022).

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

Outer carton

- Invented name qualifier: 'Comirnaty' (initially proposed without qualifier), instead of 'Comirnaty Original/Omicron BA.1' (agreed during evaluation).
- Strength: '15/15 micrograms/dose' (initially proposed)', instead of '(15/15 micrograms)/dose' (agreed during evaluation with brackets).
- MA number with 'XXX' placeholder, instead of MA number will be used after approval
- Common name/INN: common name 'COVID-19 mRNA Vaccine (nucleoside modified)' (initially proposed), instead of common name 'COVID-19 mRNA Vaccine (nucleoside modified)' and INN 'tozinameran/riltozinameran'' (during evaluation).

Box label

- Invented name qualifier: 'Comirnaty' (initially proposed without qualifier), instead of 'Comirnaty Original/Omicron BA.1' (agreed during evaluation).
- Strength: '15/15 micrograms/dose' (initially proposed)', instead of '(15/15 micrograms)/dose' (agreed during evaluation with brackets).
- MA number with 'XXX' placeholder, instead of MA number will be used after approval
- Common name/INN: common name 'COVID-19 mRNA Vaccine (nucleoside modified)' (initially proposed), instead of common name 'COVID-19 mRNA Vaccine (nucleoside modified)' and INN 'tozinameran/riltozinameran'' (during evaluation).

Vial label

- Invented name qualifier: 'Comirnaty' (initially proposed without qualifier), instead of 'Comirnaty Original/Omicron BA.1' (agreed during evaluation).
- INN or common name: 'tozinameran/riltozinameran' (INN initially proposed), instead of ''COVID-19 mRNA Vaccine' (agreed during evaluation).

8. Overall conclusion and impact on the benefit/risk balance

Introduction

BNT162b2 (Comirnaty, "Original") 30 µg is administered intramuscularly (IM) as a primary series of two doses given 3 weeks apart to individuals ≥12 years of age. Booster doses of Comirnaty 30 µg may be administered to individuals ≥12 years of age. The sequence coding for the spike protein in the present vaccine (termed "original" below) is based on that of the Wuhan strain.

The applicant is seeking the approval of a bivalent vaccine including 15µg of the original vaccine variant, and 15µg of a variant encoding the omicron BA.1 spike protein sequence. Apart from this, the products are considered similar. The sought indication is similar to the that of the Original 30µg variant:

"Comirnaty Original/Omicron BA.1 15/15 micrograms per dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older."

However, in section 4.2. of the proposed SmPC, it is clear that the applicant's intended use is for booster only (not for primary series).

Disease or condition

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

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

It is generally considered that protection may be optimised by a vaccine with a sequence that is as close to the circulating variant as possible. Moreover, it is hypothesised that a booster vaccine based on a variant virus strain will result in broader immunity against SARS-CoV-2. To optimize vaccines in the present situation, regulatory bodies (ICMRA) and WHO have suggested that a bivalent vaccine including both original as well as an omicron variant may be desirable.

Main clinical studies

The MAH has conducted clinical studies with variant vaccine mono- and bivalent (Original/BA.1) candidates including mRNA transcribing Omicron variant S protein.

This application concerns a booster dose with a bivalent original/Omicron (BA.1) vaccine, (BNT162b2 Original 15 µg + BNT162b2 OMI 15 µg = Original/BA.1 15/15 µg), given ≥4 months after the third dose to subjects≥12 years of age.

The application is based primarily on clinical data from Study C4591031 Substudy E, investigating the safety and immune responses following a fourth dose of vaccine, in approximately 1840 older adult (>55 years of age) participants. Bivalent vaccines Original/BA.1 15/15 µg, Original/BA.1 30/30 µg, monovalent BA.1 at 30 µg and 60 µg; and Original 60 µg were compared to approved Original

Comirnaty 30 µg. In this substudy, all subjects had previously received 3 doses of Original Comirnaty 30 µg.

Supportive data are provided from Study C4591031 Substudy D investigating safety and immunogenicity of an investigational monovalent Omicron BA.1 vaccine where 640 subjects aged 18-55 years (majority 30-55 years, 13% were 18-<30 years old) were randomized to receive either the monovalent BA.1 30µg (n=315) or the authorized Original 30µg (n=325) as a fourth dose. In this substudy also, all subjects had previously received 3 doses of Original Comirnaty 30µg.

Both substudies had as its primary objective investigation of the immunogenicity of different Omicron containing vaccine formulations as a fourth dose compared to a fourth dose of Original 30 µg.

The primary endpoint of these studies was to show that the novel vaccine formulations, containing the Omicron strain can induce superior immune responses to the Omicron BA.1 virus variant, and induce non-inferior response to the reference strain compared to Original 30 µg.

There is currently no immunological correlate of protection established for Covid-19, and therefore the relevance of numerical titre differences, in terms of impact on protection against severe disease or any clinical disease, cannot be determined.

The serological comparison is considered acceptable as efficacy has been demonstrated in clinical studies and neutralizing antibodies are considered an acceptable surrogate endpoint for efficacy. As stated above, it is assumed that efficacy against a new variant will be at least comparable and possibly superior, if superior levels of neutralizing antibodies are detected following booster with a variant vaccine compared to the original vaccine. The quantification of such incremental effects, however, will need to be based on real-world evidence, given that no randomised controlled trial of the variant-adapted vaccine against the original vaccine is required, according to generally agreed regulatory policy (ICMRA).

Substudy E contained 6 study arms. In each arm approximately 230 individuals received either 1) Original 30µg, 2) Original 60µg, 3) BA.1 30µg 4) BA.1 60µg 5) Original/BA.1 15/15 µg, 6) Original/BA.1 30/30µg. The fourth dose was given median 6.3 months (4.7-12.9) from the third dose. Blood samples for immunogenicity evaluations were collected on the vaccination day (baseline) and 1 month after fourth dose. The study was not designed to investigate vaccine efficacy; however, subjects were to report any symptoms that might be due to COVID, which would prompt PCR testing.

For substudy D, results have been reported for two study interventions with monovalent vaccines: Original 30µg, and BA.1 30µg.

In both substudy D and E, reactogenicity and use of antipyretic/pain medication was recorded for 7 days after administration of each dose by using an e-diary. After each dose administration, AEs were collected for 1 month and SAEs for 6 months. Acute reactions were recorded as immediate if they occurred within 30 min after administration of the vaccine.

The immunogenicity results were based on validated assays for 50% SARS-CoV-2 neutralizing titers for the original virus strain (USA-WA1/2020) and Omicron B.1.1.529 subvariant BA.1. Neutralization of Omicron variant BA4/BA5 was not studied using this validated assay but in a smaller study population including 100 individuals in both Original/BA.1 15/15 µg and Original 30µg using unvalidated methods.

Favourable effects

In Substudy E superior immune responses (lower limit of the 2-sided 95% CI for the Geometric Mean Ratio (GMR) is >1) to the Omicron BA.1 strain was demonstrated for all 4 novel Omicron strain containing vaccine formulations in comparison to the approved Comirnaty 30 µg 1 months after fourth dose. The GMR for Original/BA.1 30 µg vs. the approved Original 30 µg was 1.56 (95% CI 1.45, 2.68).

Compared to the pre-boost titre, the antibody titre against Omicron BA1. strain increased 9.1- (7.3,11.2) fold after bivalent Original/BA.1 15/15 µg vaccine and 5.8- (4.6, 7.2) fold after Original 30µg vaccine.

The sero-response rate of Original/BA.1 30µg was 71.6 % versus 57 % for Original 30µg, demonstrating statistically significant superiority (difference 14.6 % (4.0, 24.9), pre-defined criteria >-5%).

Noninferiority based on the GMR for reference strain response was met by both bivalent vaccine groups as the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion). The GMR for Original/BA.1 30µg vs. the approved Original/BA.1 was 0.99 (0.82, 1.2). Compared to pre-boost titres, the antibody titer against Wuhan Strain increased 4.3-fold after both vaccines.

The sero-response rate for Original/BA.1 30 µg against the reference strain was 50 %, versus 49.2% for Original 30µg.

Additional descriptive analyses from Substudy E were performed to further characterize BA.4/BA.5 neutralization responses following a booster (fourth) dose. A total of 100 participants were randomly selected from each vaccine group in the expanded cohort. Demographic characteristics for participants in this subset were similar between the two vaccine groups. The observed Omicron BA.4/BA.5 neutralizing GMTs at one-month post-Dose were numerically slightly higher for the bivalent Original/BA.1 group compared to Original 30 µg group (167.4 vs 155.1). Overall, GMFRs (4.5 vs 3.3) and seroresponse (56% vs 42%) followed this trend.

Also, immunological response to Omicron BA.2.75 strain was investigated in 30 randomly selected individuals from both Original/Omicron BA1 15/15 µg and original arms from Substudy E. Overall, the observed Omicron BA.2.75 neutralizing GMTs at 1-month post-Dose in participants without evidence of infection were numerically slightly higher for the bivalent Original/Omicron BA.1 15/15 µg group compared to Original group (108.0 vs 88.8).

Each study arm had about 230 subjects. In the expanded cohort, cases in a total of 30 cases of COVID-19 across all vaccine groups were accrued up to the data cutoff date of 16 May 2022.

Original 30 µg and 60 µg groups: 7 and 6 cases, respectively; Omicron BA1. 30 µg and 60 µg groups: 7 and 3 cases, respectively; Original/BA1. 15/15 µg and 30/30 µg groups: 1 and 6 cases, respectively.

No cases meeting severe criteria per the FDA or CDC definition were observed in any of the vaccine groups.

In substudy D approximately 640 participants ≥18 to ≤55 years of age received a fourth dose of either approved Original 30 µg or monovalent BA.1 30 µg about 4 month after the third dose. Superior immunogenicity to omicron BA.1 and non-inferior response to reference strain were demonstrated for BA.1 30 µg compared to the original vaccine.

Uncertainties and limitations about favourable effects

The submitted studies were not designed to study vaccine efficacy. However, breakthrough COVID-19 cases were captured by protocol. The study was performed in the US during 1-2Q 2022, when presumably BA.1 and BA.2 was circulating. Breakthrough infections occurred in all study arms. It remains uncertain to what extent the increase in neutralising titres against BA.1 would translate into increased protection against severe disease or against clinical disease, compared to the presently approved vaccine.

Immune responses are generally stronger in younger people compared to older. Therefore, one can extrapolate that the booster effect of Original/BA.1 30µg against the BA.1 strain will be seen also in

younger people, although data are only available from the abovementioned substudy D. In this a monovalent BA.1 vaccine at 30 µg elicited stronger responses against BA.1, compared to Original 30µg. Whether the relative numerical increment in efficacy of Original/BA.1 compared to Original will be seen also for adults younger than 55, however, is unknown. These considerations are relevant also for adolescents 12-18 years of age.

The data on immunogenicity against BA.5. were obtained with non-validated FFRNT assay. Moreover, it is not known if the numerically small increase in neutralising titres compared to that of the original product will be associated with improved relative efficacy

No information about antibody kinetics over time after the fourth dose has been submitted.

The current application only contains data on the use of Original/Omicron BA.1 15/15 µg for a fourth total dose of Comirnaty. However, it is not anticipated that it would be in any way inferior to use the bivalent vaccine instead of the monovalent original vaccine for the third dose, or after four previous doses. It can also be anticipated that the bivalent vaccine could be used for booster regardless of the number of previous doses, once the two doses of primary vaccination have been given.

Duration of protection is presently unknown, as is the future epidemiological situation with respect to variants.

The applicant suggests the approved use of Original/Omicron BA.1 15/15 µg after a primary series of any Covid-19 vaccine. However, data are only available after a primary series of Comirnaty. While the absence of data results in some uncertainty, it is likely that a clinically relevant boosting effect would be seen regardless of what vaccine was used for primary vaccination.

Unfavourable effects

The safety database of substudy E consists of 1841 individuals aged 55 years and above, who were followed up with solicited reactogenicity event reporting as described above. Of these 305 received Original/BA.1 15/15 µg.

Pain at injection site was the most frequently reported local reaction in all study groups in *substudy E*. (58% Original/BA.1 15/15µg; 60% Original 30µg; 68% Original/BA.1 30/30µg). The majority of the local reactions were mild to moderate in severity. No grade 4 reaction were reported.

The most frequently reported systemic reaction was fatigue for all tested vaccine variants (49% Original/BA.1 15/15µg; 45% Original 30µg; 57% Original/BA.1 30/30µg), followed by headache (34% Original/BA.1 15/15µg; 27% Original 30µg; 37% Original/BA.1 30/30µg), muscle pain (22% Original/BA.1. 15/15µg; 20% Original 30µg; 28% Original/BA.1 30/30µg), joint pain (11% Original/BA.1 15/15µg; 9% Original 30µg; 19% Original/BA.1 30/30µg) and fever (5% Original/BA.1 15/15µg; 4% Original 30µg; 8% Original/BA.1 30/30µg).

Four events of fever >38,9-40°C were reported in the group that received Original/BA.1 15/15µg vaccine, whereas none in the Original 30µg reported fever >38,9°C. The only event of fever >40,0°C was reported by a subject that received BA.1 60µg, in that group four events of fever >38,9-40°C was also reported. Most of the systemic reactions in all groups were mild to moderate with a median time to onset of 2 days and resolved within a median time of one day.

In *substudy E*, antipyretic or pain medication were used at similar frequency for the subject that received Original/BA.1 15/15 µg (29%) as for the subject that received Original 30µg (27%).

No clinically relevant differences were noted in terms of local and systemic reactions in *substudy E* across all vaccine groups when evaluated by subgroups of race, ethnicity and baseline SARS-CoV-2 status. There was a tendency to a slightly higher frequency reactogenicity reported among female

subjects in all study arms, there was however no difference in severity and most of the events were mild or moderate. A similar trend was observed in the placebo-controlled phase 2/3 study C4591001 for Original 30µg, where the same pattern was also noted in the placebo group.

The local and systemic reactions reported among subjects >55 years of age that have received Original/BA.1 15/15µg in substudy E are reflected in the proposed section 4.8 of the SmPC.

The rate for any AEs up to the cut-off date for Original/BA.1 15/15µg was within the range seen for all tested vaccine variants (6.2%; (range; 3.9% (BA.1 60µg)-10.4% (Original/BA.1 30/30µg)). There were no AEs that led to death.

Whereas there are safety data available for Omicron/BA.1 in those 55 years or older, the safety of a BA.1 vaccine variants in younger subjects has only been directly demonstrated in *substudy D*, for a monovalent vaccine at 30µg. The safety database from this study contained 640 individuals aged 18-55 years randomised 1:1 to Original/BA.1 30µg or to Original 30µg, who were followed up as described above.

In *substudy D*, pain at the injection site was the most common local reaction in both the BA.1 30µg and the Original 30µg arm (78% each). Fatigue was the most reported systemic reaction (64% BA.1 30µg; 60% Original 30µg), followed by headache (48% BA.1 30µg; 45% Original 30µg), muscle pain (34% BA.1 30µg; 28% Original 30µg) and fever (9% BA.1 30µg; 6% Original 30µg).

Most of the events were mild or moderate in severity and no Grade 4 systemic events were reported.

Overall, the emerging safety profile is similar to that of Original 30ug. No new safety concerns have emerged. There were no cases of myocarditis.

Uncertainties about unfavourable effects

Overall, the size of the safety database for BA.1 containing variant vaccines is not large enough to characterise the frequency of rare adverse events. However, it is notable that the only difference between Original/BA.1 and Original, lies in the spike protein sequence of BA.1.

Across studies, there is a tendency for numerically slightly higher frequencies of reactogenicity-related events with BA.1 containing vaccines. However, these differences are marginal and not deemed clinically meaningful.

While reactogenicity and safety data are available for the bivalent Original/BA.1 vaccine variant in subjects aged 55 and higher, data are only available for a monovalent BA.1 vaccine variant at 30ug in subjects below this age. However, based on (a) a similar total dose of mRNA, (b) no relevant differences in reactogenicity between Original and Original/BA.1 in those aged above 55, and (c) no relevant differences in reactogenicity between Original and BA.1 in those below 55, the inference may be drawn that reactogenicity will be acceptable also in those below 55.

There are no data on the bivalent Original/BA.1 variant vaccine in pregnancy. However, the total mRNA dose is the same as for Original, and reactogenicity is similar. Moreover, the only difference between products lies in the spike protein sequence. Therefore, a conclusion of acceptable safety in pregnancy and breast-feeding may be drawn for the vaccine variant.

There are no safety data for the use of Original/Omicron BA.1 15/15 as a third dose in total, as a fifth dose in total, or after a primary series with another Covid-19 vaccine. Moreover, there are no safety data for a repeat booster with Original/Omicron BA.1 15/15. However, there are no reasons to believe that the safety profile would differ substantially in any of these scenarios as this was not seen for the original.

Summary considerations

While protection against severe Covid-19 remains relevant with the Original Comirnaty, efficacy against symptomatic disease due to omicron is clearly lower than was the case for the previous dominant variants. Based on the principles of immunology, greater protective efficacy may be conferred the closer a Sars-Cov-2 vaccine is to the circulating variant. Moreover, it is anticipated that Sars-Cov-2 will continue to evolve, and that an increased breadth of immunity is valuable. Therefore, a bivalent vaccine has been deemed desirable by regulatory bodies and public health authorities.

The applicant has demonstrated that a bivalent Original/BA.1 vaccine at 15/15ug confers greater immunogenicity against BA.1, compared to the approved Original alone. While the precise size of any incremental efficacy (protection against clinical disease) is unknown, it appears reasonable to update vaccine composition as the virus evolves, analogous to what is done with influenza.

While it is recognized that BA.1 is presently no longer the dominant strain, the present update is seen as a likely first step, where vaccine development will trace the evolution of the virus. Vaccine effectiveness will be followed in observational cohorts, which will also be used to understand breath of coverage and duration of protection.

The reactogenicity of BA.1 containing vaccines do not differ substantially from Original, provided that the total mRNA dose is the same. While data for the bivalent vaccine are only available in those above 55, a monovalent BA.1 vaccine variant was studied in younger adults, also yielding a clinically similar reactogenicity profile. Consequently, a substantially different safety profile in adolescents or younger adults, compared to the available Comirnaty Original, is considered sufficiently unlikely to permit approvability.

The Omicron/BA.1 15/15µg variant is presently under study in subjects 18-55 years of age. The applicant has committed to deliver the immunogenicity and safety results of this trial, as a post-marketing commitment.

There are no data to support the use of this product for primary vaccination. Therefore, it should be clear from the indication statement that use is only for subjects that have completed a primary vaccination series.

Based on cumulative experience of mRNA vaccines, it is sufficiently likely that a relevant boosting effect will be seen regardless of what vaccine was used for the primary vaccination series. Given the variability of primary series and boosters that have been given to EU patients, there is a need for flexibility. Therefore, it is agreed that the product may be used for boosting regardless of which prior vaccinations, and that no restrictions are needed with respect to the specifics of prior vaccinations.

Moreover, safety and immunogenicity are not likely to differ substantially if the product is given as a repeat booster, as long as a sufficient interval between doses is maintained. This has previously been determined to at least 3 months for Comirnaty. Whether or not to use this particular product for a repeat boost, would depend on the epidemiological situation and observational data indicating waning immunity.

Based on the above considerations, the following indication is proposed:

Comirnaty Original/Omicron BA.1 (15 micrograms/15 micrograms)/dose dispersion for injection is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older who have previously received at least primary vaccination against COVID-19. (See sections 4.2 and 5.1.)

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

In summary, the B/R for the Original/BA.1 15/15µg could be positive in adolescents 12 years and above, and adult subjects, provided that the indication statement is adjusted in line with what is suggested above. Moreover, the conditions for use per SmPC need to be agreed, solving the above-mentioned issues.

The benefit-risk balance of COMIRNATY remains positive.

9. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
B.I.a.6.a	B.I.a.6.a - Changes to the active substance of a vaccine against human coronavirus - Replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine	Type II	I, IIIA, IIIB and A

Addition of a new strain (Omicron BA.1) resulting in a new Comirnaty bivalent Original/Omicron BA.1 (15 µg tozinameran/ 15 µg riltozinameran per dose) dispersion for injection presentation. The SmPC, the Package Leaflet and Labelling are updated accordingly. A revised RMP version 6.1 has been approved.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA, IIIB and A and to the Risk Management Plan are recommended.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. Please add this product to the current EURD list entry: 10898 and re-name the entry: tozinameran (COMIRNATY), tozinameran/riltozinameran (COMIRNATY Original/Omicron BA.1).

Table on conditions and recommendations

Area	**Number**	**Description**	**Classification**	**Due date**
Quality	1	The expressed protein size for BNT162b2 Omicron (B.1.1.529) DS is evaluated by western blot. The Applicant claims that the protein size is consistent with the expected size of the translated protein. However, the theoretical protein sizes of the mature protein and variants	REC	Q4/2022

Area	Number	Description	Classification	Due date
		thereof are not presented in the dossier. This information should be provided, and the bands observed by WB should be assigned. In addition, the antibody used for western blot should be further described, i.e., it should be stated if it targets the S1 or S2 domain of the protein. The dossier should be updated accordingly.		
Quality	2	The MAH should reassess and optimise the proposed specification for the RNA ratio, when a sufficient number of BNT162b2 Bivalent (Wildtype and Omicron) Finished Product batches have been manufactured.	REC	Q2/2023

10. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

For more information, please refer to the Summary of Product Characteristics.