EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: COMIRNATY Original/Omicron BA.4-5

International non-proprietary name: tozinameran and famtozinameran

Procedure No. EMEA/H/C/005735/II/0143

Marketing authorisation holder (MAH) BioNTech Manufacturing GmbH

Note

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

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List of abbreviations

Abbreviation	Definition
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

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 26 August 2022 an application for a variation.

The following variation was requested:

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.4-5) resulting in a new Comirnaty bivalent Original/Omicron BA.4-5 (15 µg / 15 µg per dose) dispersion for injection presentation. The SmPC, the Package Leaflet and Labelling are updated accordingly. The submission includes a revised RMP version 7.0.

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 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 (BA.4/BA.5) as a variant of concern (VOC) is the subject of this variation. To assist in the public health crisis, a new 30 µg BNT162b2 Bivalent [Original and Omicron (BA.4/BA.5) variant] finished product (herein referred to as Bivalent), consisting of the Original and Omicron (BA.4/BA.5) active substances strains (also referred to as active substance construct), is being introduced to the MAA as a new variant vaccine.

The Bivalent vaccine is manufactured by mixing two active substance 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 famtozinameran 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).

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

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 – Tozinameran

The active substance tozinameran is already approved for the original Comirnaty vaccine formulations (EU/1/20/1528/001-005). No changes to the information related to tozinameran are proposed.

3.3 Active substance – Famtozinameran

General information (CTD module 3.2.S.1)

Section 3.2.S.1 has been updated with information related to the Omicron BA.4/BA.5 variant. The information provided is considered adequate and acceptable.

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/1/20/1528/001-007) for the manufacture of the active substances tozinameran (Original) and riltozinameran (Omicron BA.1). The GMP compliance of these sites has been previously confirmed.

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

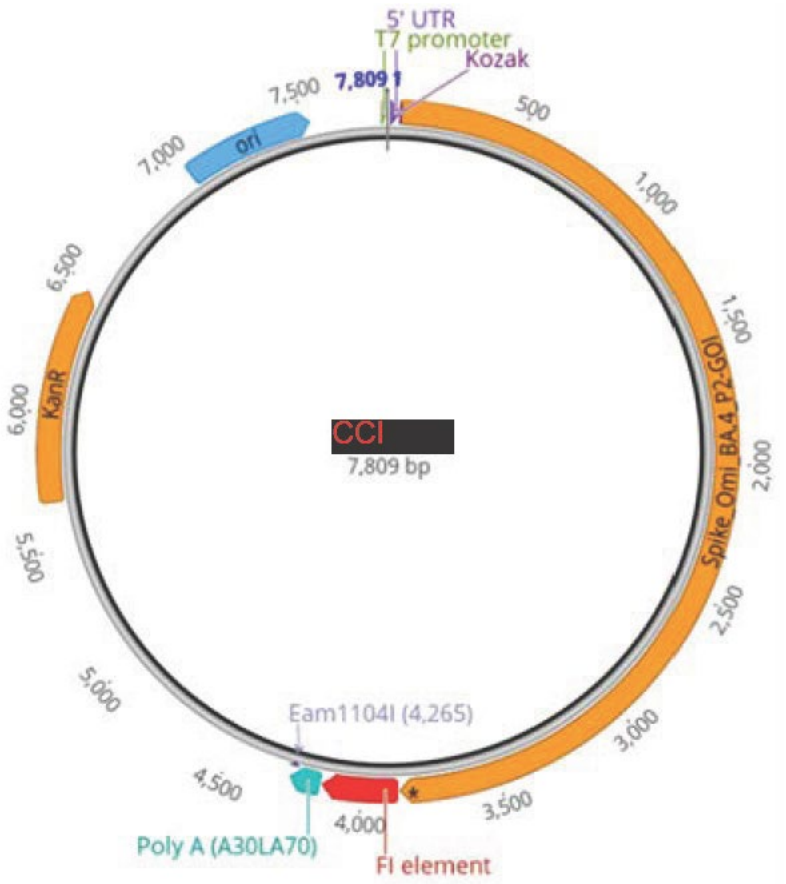
The manufacturing process and process controls are the same as currently approved for the manufacture of tozinameran and riltozinameran.

Control of materials (CTD section: S.2.3)

2.3.S.2.3.2. Control of Materials - Source, History and Generation of Plasmids

Manufacture of the BNT162b2 Omicron BA.4/BA.5 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 Escherichia coli cells. The plasmid is a 7,809 base pair plasmid designed for the production of Omicron BA.4/BA.5 variant.

Figure 3.2.S.2.3-1. Omicron BA.4/BA.5 Plasmid Map



BNT162b2 Omicron (BA.4/BA.5) variant vaccine active substance is manufactured by in vitro transcription using a linear DNA template, produced via plasmid DNA from transformed Escherichia coli cells. The functional elements of the Omicron (BA.4/BA.5) plasmid are sufficiently described in graphic and tabular formats and the sequence is included. The source and generation of the Omicron (BA.4/BA.5) 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 the 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. At the time of the submission, results for the restriction map analysis and plasmid copy number are still pending. 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 GF4643 manufactured at Pfizer Chesterfield. Information on WCBs will be added at a later date once data is available. The MAH is requested to provide a timeline for the intended implementation of WCBs. The plasmid MCB is enrolled in a cell bank stability program consisting of viability and plasmid retention assays conducted at all stability time points. The strategy is considered adequate.

The Omicron (BA.4/BA.5) plasmid is manufactured by a fed-batch fermentation process initiated from the bacterial master cell bank, identical to the process described for the original plasmid 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 one batch are provided for the circular and linearized plasmid. All analytical methods used for the control of the linear DNA template obtained from Omicron (BA.4/BA.5) plasmid are identical to the already provided methods used for testing of the original plasmid DNA template except for the identity by restriction mapping and identity of the transgene region by DNA Sanger sequencing methods. The ID by restriction mapping method was updated to remove the use of a reference standard and the ID by Sanger sequencing method was updated to include Omicron-specific reagents. Summaries of the validation exercise are included and considered adequate.

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 (BA.4/BA.5) circular plasmid DNA and linearized DNA. Only T0 data results are currently available for the specific Omicron (BA.4/BA.5) 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.

Working cell banks for the manufacturing of the BNT162b2 Omicron (BA.4/BA.5) DS will be established based on reviews if demand forecast for future manufacturing plans. When the need arise, WCBs will be manufactured from the MCB GF4643 and relevant information will be submitted to EMA for review. This is found acceptable.

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 and riltozinameran.

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 (BA.4/BA.5) active substance. To date, one small scale and one large scale batch have been manufactured.

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.

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 (BA.4/BA.5) active substance manufacturing process. The CPPs, IPT-Cs and IPT-Ms are the same as those defined for the approved variant and 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 from solely one batch demonstrate that the first Omicron (BA.4/BA.5) manufactured at commercial scale complies with the active substance specification. However, consistency in manufacturing of the Omicron (BA.4/BA.5) variant active substance has not yet been demonstrated.

The absence of comparability data is found acceptable since the Omicron (BA.4/BA.5) variant constitutes a new active substance. However, comprehensible characterisation of the Omicron variant should be provided, as requested in section 3.2.S.3.

Characterisation (CTD module 3.2.S.3)

The Applicant has provided characterisation data for the Omicron (BA.4/BA.5) 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. The results for primary structure, 5'-Cap structure and higher order structure are found acceptable, sufficiently supporting the expected characteristics of the Omicron (BA.4/BA.5) variant.

Biological activity is confirmed by cell-free in vitro translation and western blot analysis using either horseradish peroxidase-conjugated streptavidin (SA-HRP) or an antibody specific for the SARS-CoV-2 spike protein. The method as such is found acceptable. It is observed that, as compared to the characterisation of the original variant and the Omicron (BA.1) variant, the assay involving transfection into HEK-293 cells has been excluded. This is found acceptable since cell-free in vitro translation followed by WB analysis would sufficiently reflect expressed protein size.

The bands observed by Western blot, using either of the antibodies, are considered very broad. The results from the analysis do not support that a target protein of solely one size is expressed. Since cell-free in vitro translation is used, variation in protein size due to post-translational modifications can be excluded. Further clarification regarding the identity of the observed bands is requested.

The expressed protein size for BNT162b2 Omicron (BA.4/BA.5) active substance is evaluated by western blot following in vitro translation. From the data presented it cannot currently be concluded that the protein size is consistent with the expected size of the translated protein and additional information should be provided. The Applicant has committed to update Section 3.2.S.3.1 to include theoretical protein sizes of the mature protein and variants thereof. The information will be submitted

by the end of 2022, which is in line with the commitment for the Omicron BA.1 variant. In addition, the dossier should be updated with a figure on BNT162 Omicron (BA.4/BA.5) Expressed Protein Size by In Vitro Translation, as detected by western blot and as provided in response to the request for supplementary information. This is found acceptable as a recommendation for future quality development **(REC1)**.

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

The specification for Famtozinameran (Omicron (BA.4/BA.5)) 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 (ddPCR, 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 (BA.4/BA.5) variant active substance follows the specification established and approved for the original variant and therefore is considered adequate.

Analytical procedures for Omicron (BA.4/BA.5) variant active substance 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 two new methods are included, one based on droplet digital polymerase chain reaction (ddPCR) in alignment with the identity method used for the bivalent Comirnaty products, and one based on reverse transcriptase quantitative polymerase chain reaction (RT-qPCR), introduced to alleviate capacity constraints within the testing network. 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 (BA.4/BA.5) variant, the approach is endorsed. The newly introduced methods are sufficiently described. Validation exercises have been performed at the relevant sites. These methods can be used as duplex or single plex reactions and specificity has been demonstrated for different primer pairs able to identify a number of mRNA variants, including the WT, BA1.2 and BA.4/5 variants.

Batch results are presented for in total three active substance batches; one batch used for clinical trials, process confirmatory studies, and stability studies and two commercial batches. All specification acceptance criteria in place at the time of release are met. The specification and limits for Omicron (BA.4/BA.5) variant active substance are based on the BNT162b2 original active substance. 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 standards are the same as currently approved for tozinameran and riltozinameran.

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

The container closure system is the same as currently approved for tozinameran and riltozinameran.

Stability (CTD module 3.2.S.7)

The proposed shelf-life for the Omicron BA.4/BA.5 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 one Omicron batch is on-going. No stability data on this batch has been submitted in section 3.2.S.7. The Applicant commits to provide long term and accelerated stability data for the 1-month time point by the middle of November as the active substance batch GH5745 was recently placed on stability and no additional time point past T = 0 is available. Since batch GH5745 was manufactured 17 July 2022, the strategy is not understood. One-month data should be available by now. However, submission of stability data in November is found acceptable as a recommendation for future quality development. **(REC 2)**

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 and omicron (BA.4/BA.5) 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.4/BA.5), 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 (Construct 1)	In-house specification	Active ingredient	0.05	113 µg	15 µg
BNT162b2 Omicron (BA.4/BA.5) drug substance (Construct 2)	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
N/A = Not applicable

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

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

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

Pharmaceutical development (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 (BA.4/BA.5) 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.4/BA.5), is present at approximately 15 µg/dose.

Two active substances are utilized in the bivalent vaccine, the original active substance and omicron (BA.4/BA.5) active substance. 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.

A revised QTPP has been developed for the bivalent vaccine. 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 (BA.4/BA.5) Variant] 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	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
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	
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 BA.4/BA.5 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.	
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)
Safety		

Product Element	Product Quality and Performance Characteristics	Quality Attributes
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.

Furthermore, information has been provided to demonstrate that physicochemical characteristics are similar across the active substances and are not impacted by minor changes in mRNA sequence or length associated with a new construct. As the solution properties of the active substances are similar, data provided in Table P.2-2 provides additional evidence that data collected using Omicron BA.1 in a bivalent vaccine can be considered representative of expected results for a bivalent vaccine containing Omicron BA.4/BA.5. This is also agreed to.

A development history and lot genealogy and usage of the bivalent vaccine has been provided. An initial supportive clinical finished product lot (22-DP-01216, Pfizer Andover) and a commercial scale confirmatory finished product lot (GH9545, Pfizer, Puurs) has been manufactured.

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 active substance 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 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. 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 as well as via extended characterization testing including studies of size distribution and particle shape (AF4-MALS-QELS), surface charge (zeta potential) and surface PEG (one-dimensional proton NMR spectroscopy). Comparability has been sufficiently demonstrated between the bivalent vaccine finished product and the original vaccine finished product and this conclusion is valid for both the bivalent vaccine finished product including the original and omicron BA.1 strains and bivalent vaccine finished product including the original and omicron BA.4/BA.5 strains.

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 (GH9545) and a supportive clinical finished product lot (22-DP-01216). Both these batches met the specification acceptance criteria in place at the time of testing. The applicant commits to update section P.5.4 with the batch data for the batches GH9545 and 22-DP-01216 during the procedure. 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 for three lots of the bivalent vaccine finished product including the original and omicron BA.1 strains, results presented in variation Comirnaty II-140. For this variation Comirnaty II-143, the applicant argues that no mixing data are needed for the bivalent vaccine including original and omicron BA.4/BA.5 strains due to the fact that the active substance physicochemical properties are similar across the original, omicron BA.1, and omicron BA.4/BA.5 strains and therefore, the data collected to support the bivalent original and omicron BA.1 finished product is considered applicable to the bivalent original and omicron BA.4/BA.5 variant finished product. In addition, the applicant has provided two additional commercial scale batches of DP where the RNA ratio remains within 2% of the target value of 1:1 for the RNA ratio. 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. See section 3.2.P.5 for assessors comments.

Sections P.2.4, P.2.5 and P.2.6 have not been updated for the bivalent BA.4/BA.5 vaccine (procedure no EMEA/H/C/005735/II/0143) compared to the bivalent BA.1 vaccine (procedure no EMEA/H/C/005735/II/0140).

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. See section 3.2.P.7 for further information.

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 in section P.2.3, P.2.4, P.2.5 and P.2.6 is found sufficient and acceptable.

Manufacture (CTD module 3.2.P.3)

The bivalent BA.4/BA.5 vaccine is manufactured at manufacturing sites, and using the same platform process, as currently approved for the original Comirnaty Tris/Sucrose vaccine formulation (EU/1/20/1528/002-005), including the LNP bulk manufacturer Allergopharma added for the original Tris/Sucrose vaccine in variation EMEA/H/C/005735/II/0134/G. The GMP compliance of these sites has been previously confirmed.

The manufacturing process consist 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.4/BA.5) 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 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 BA.4/BA.5 vaccine. A mixing study to evaluate homogeneity is performed and data are provided in section P.2.3. Three batches of the bivalent BA.1 vaccine were studied at the beginning, middle and end of the filling process confirming a homogeneous mixing of original and omicron BA.1 strains. The results are presented in variation EMEA/H/C/005735/II/0140 for the bivalent BA.1 vaccine. No mixing data are provided for the bivalent BA.4/BA.5 vaccine. This is found acceptable provided that additional data to confirm homogeneity for the bivalent BA4/BA.5 vaccine is provided.

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

The bivalent BA.4/BA.5 vaccine uses 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).

The comprehensive set of relevant tests with corresponding acceptance criteria and are based on those established for the original finished product for the majority of the test attributes. The acceptance criteria for release and stability testing of the bivalent finished product are the same as for the original vaccine for all quality attributes except for the RNA ratio that is related to the mixing of the original and omicron (BA.4/BA.5) strains.

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 which, however, is not supported by the submitted batch data. No additional justification is provided. It is acknowledged that the experience is limited to one finished product lot, manufactured from one active substance batch, and the current specifications provide adequate assurance on the ratio. Therefore, when a sufficient number of BNT162b2 Bivalent vaccine (Wildtype and Omicron BA.4/BA.5) 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. **(REC 3)**

In the control of BNT162b2 Bivalent (Wildtype and Omicron BA.4/5) 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 (25%-75%) and specificity. Furthermore, the method is currently transferred from Pfizer-ARD to BioNTech Manufacturing GmbH (Mainz) and BioNTech IMFS GmbH. Parameters, experimental design and acceptance criteria for the transfer exercise are provided and considered adequate. 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 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 (GH9545, Pfizer, Puurs) via a certificate of analysis, a supportive clinical batch (22-DP-01216 - Pfizer Andover) as well as for two additional commercial scale batches (GH9702 and GJ5342). All results provided met the acceptance criteria at the time of release. The applicant has updated section P.5.4.

In addition, stability studies have been initiated for the supportive batch 22-DP-01216 and for the confirmatory commercial scale batch GH9545.

This is found acceptable.

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

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

Therefore, the proposed shelf-life for the bivalent vaccine finished product of 12 months is agreed 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.

This is found acceptable.

Post-approval stability protocol and stability commitment

The applicant confirms that the identical Post-approval stability protocol and stability commitment in section 3.2.P.8.2 is valid for the bivalent vaccine finished product including original and omicron BA.4/BA.5 strains as for the bivalent vaccine finished product including original and omicron BA.1 strains.

This is found acceptable.

Appendices (CTD module 3.2.A)

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 MAH should provide information on the theoretical protein sizes of the mature protein and variants thereof. In addition, the MAH should update the dossier with Figure 1. *BNT162 Omicron (BA.4/BA.5) Expressed Protein Size by In Vitro Translation*, as provided in response to the request for supplementary information.
2. The MAH should provide long term and accelerated stability data for the 1-month time point for active substance batch GH5745.
3. 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. Non-clinical aspects

4.1 Introduction

With this type II variation, the MAH has submitted data from studies on immunogenicity in mice with variant vaccines, to support an approval of the BA4/BA5 bivalent vaccine. No further safety studies have been performed, since safety studies performed for the initial MAA are considered relevant for this variant vaccine, only differing in the sequence of the spike protein.

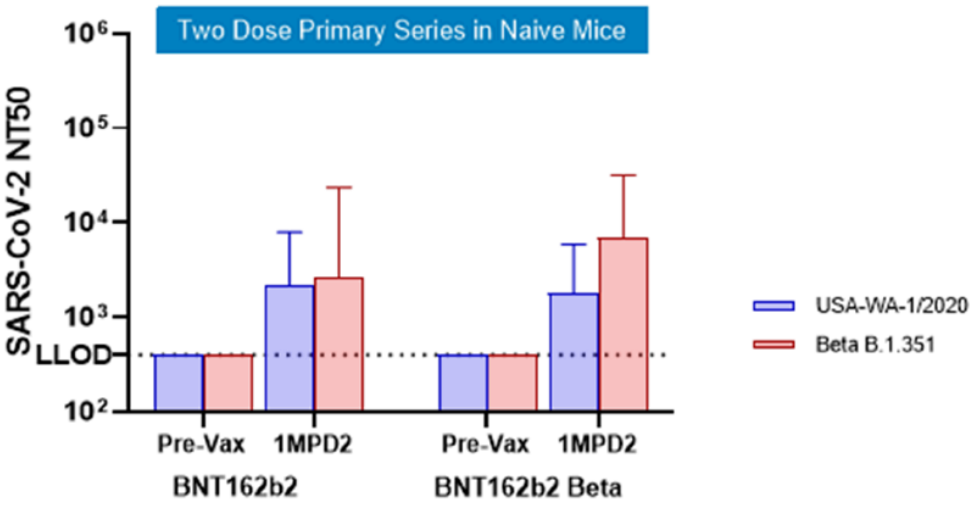
4.2 Pharmacology

Primary pharmacodynamic studies

Beta Variant-modified Vaccine

A monovalent Beta (B.1.351) variant-modified vaccine was administered to naïve Balb/c mice as a two-dose primary series and serum neutralization responses were evaluated in validated recombinant SARS-CoV-2 USA-WA-1/2020 (reference strain) and Beta variant neutralization assays. These are the same assays as were used for clinical testing of the Beta-modified vaccine (Study C4591001). The BNT162b2 Beta vaccine elicited substantial increases in Beta neutralizing titers and more modest increases in reference strain neutralizing titers following a 2-dose primary series (Figure 2.4.2-3).

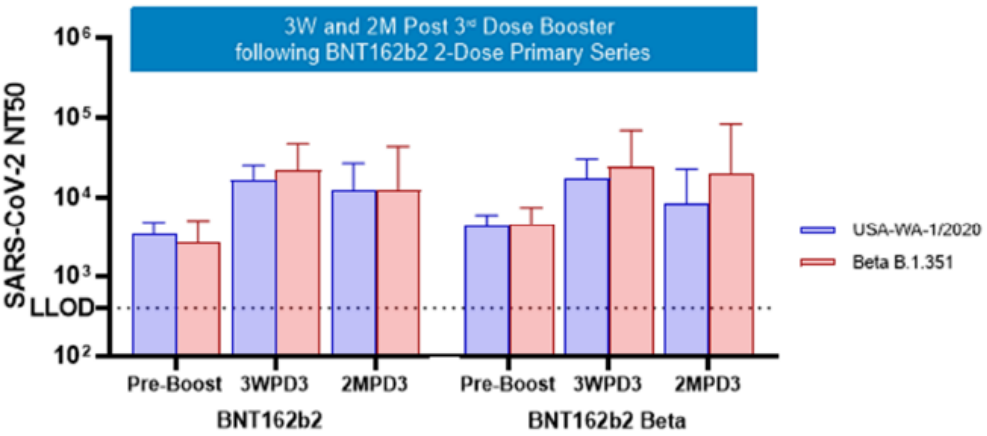
Figure 2.4.2-3. BNT162b2 Beta Vaccine Primary Two Dose Series in Naïve Balb/c Mice



Two groups of Balb/c mice (n=10/group) were immunized IM on Days 0 and 21 with 0.5 µg of the indicated LNP-formulated modRNA vaccine. Sera collected at 1 month post dose 2 (1MPD2) were tested in validated recombinant SARS-CoV-2 USA-WA1/2020 (reference strain) and Beta variant neutralization assays. Bars indicate the GMT for each group and strain and vertical whiskers within each bar indicate the 95% confidence interval. NT50, 50% neutralization titer; LLOD, low limit of detection.

The Beta-modified vaccine was also tested as a 3rd dose booster in BNT162b2-experienced mice. Reference strain and Beta neutralizing titers were substantially increased following a Beta vaccine 3rd dose booster, with a trend for higher responses elicited for the Beta variant compared to the reference strain (Figure 2.4.2-4).

Figure 2.4.2-4. BNT162b2 Beta Vaccine Third Dose/Booster in BNT162b2-Experienced Balb/c Mice



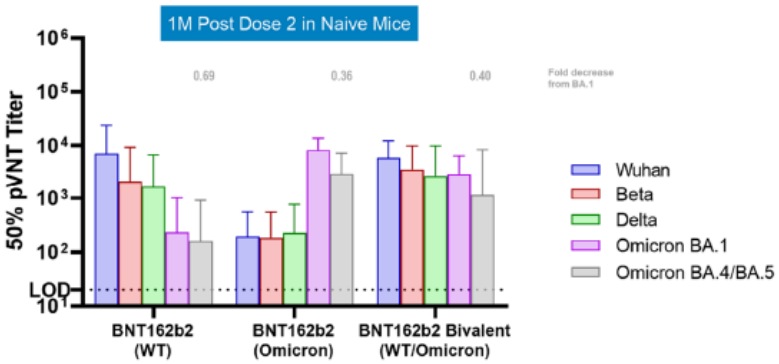
BNT162b2-experienced Balb/c mice (n=10/group; received 2 doses of 0.5 ug BNT162b2 at Days 0 and 21) were immunized IM with 0.5 µg of the indicated LNP-formulated modRNA vaccine as a 3rd dose booster 1 month after the prior BNT162b2 doses. Sera collected at 3 weeks and 2 months post dose 3 (3WPD3 and 2MPD3, respectively) were tested in validated recombinant SARS-CoV-2 USA-WA1/2020 (reference strain) and Beta variant neutralization assays. Bars indicate the GMT for each group and strain and vertical whiskers within each bar indicate the 95% confidence interval. NT50, 50% neutralization titer; LLOD, low limit of detection.

Omicron BA.1 Variant-modified Vaccine

The BNT162b2 prototype vaccine and monovalent or bivalent BNT162b2 Omicron BA.1 variant-modified vaccines were tested as a two dose primary series in naïve Balb/c mice and as a 3rd dose booster in BNT162b2-experienced Balb/c mice to assess if preclinical immunogenicity might emulate immunogenicity trends in humans. Sera were collected 1 month following a two dose primary series (Day 0 and Day 21) or 1 month after a 3rd dose and evaluated in a non-validated pseudovirus neutralization assay using VSV-pseudotyped viruses bearing the indicated SARS-CoV-2 spike.

As was observed in Study C4591031 Substudy D Cohort 3, an Omicron monovalent primary series elicited an effective but Omicron-focused response in naïve mice, with limited neutralization of other VOCs (Beta, Delta) or the Wuhan reference strain. The bivalent Omicron-modified vaccine elicited a broad neutralizing response against Omicron and other VOCs and the reference strain, suggesting a greater breadth of response against antigenically diverse SARS-CoV-2 spikes. While Omicron BA.4/BA.5 neutralizing responses were consistently lower and with a wider spread among individual animals compared to Omicron BA.1 in all vaccine groups, BA.4/BA.5 responses were significantly higher in monovalent and bivalent Omicron-modified vaccine groups compared to the BNT162b2 prototype vaccine.

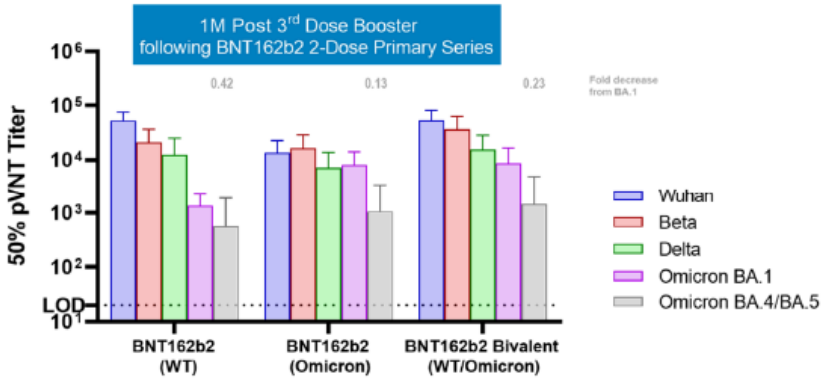
Figure 2.4.2-5. Primary Two Dose Series in Naïve Balb/c Mice



Balb/c mice (n=15/group) were immunized IM on Days 0 and 21 with 0.5 µg of the indicated LNP-formulated modRNA vaccine. Sera collected at 1 month post dose 2 were tested for SARS CoV-2 pseudovirus 50% neutralization titers (pVNT) against Wuhan reference strain, Beta, Delta, Omicron BA.1 and BA.4/BA.5. Bars indicate the GMT for each group and strain and vertical whiskers within each bar indicate the 95% confidence interval. The GMR of Omicron BA.4/BA.5 GMTs compared to Omicron BA.1 GMTs for each vaccine group are indicated in grey text above the grey bar. LOD, limit of detection.

When mice received 2 prior doses of BNT162b2 and were given a 3rd dose booster of an Omicron-modified vaccine, both monovalent and bivalent Omicron-containing vaccines provided increases in Omicron BA.1 neutralizing titers and comparable increases in Wuhan, Beta, and Delta neutralizing responses compared to the prototype vaccine. In clinical Study C4591031, reference strain and Delta neutralizing responses for Omicron-modified vaccines assessed as a 4th dose booster (in individuals that received 3 prior doses of BNT162b2) similarly demonstrated GMTs for the reference strain and Delta that were well preserved across all Omicron-modified vaccine groups. For this preclinical study, Omicron BA.4/BA.5 neutralizing titers were much reduced in all groups, with a slight trend for higher titers in the Omicron-modified vaccine groups. A similar neutralizing response profile was observed in humans, where BA.4/BA.5 was neutralized to a lesser extent compared to BA.1 with numerically higher BA.4/BA.5 neutralizing GMTs in the Omicron-modified vaccine groups.

Figure 2.4.2-6. BNT162b2 Omicron BA.1 Third Dose/Booster in BNT162b2-Experienced Balb/c Mice

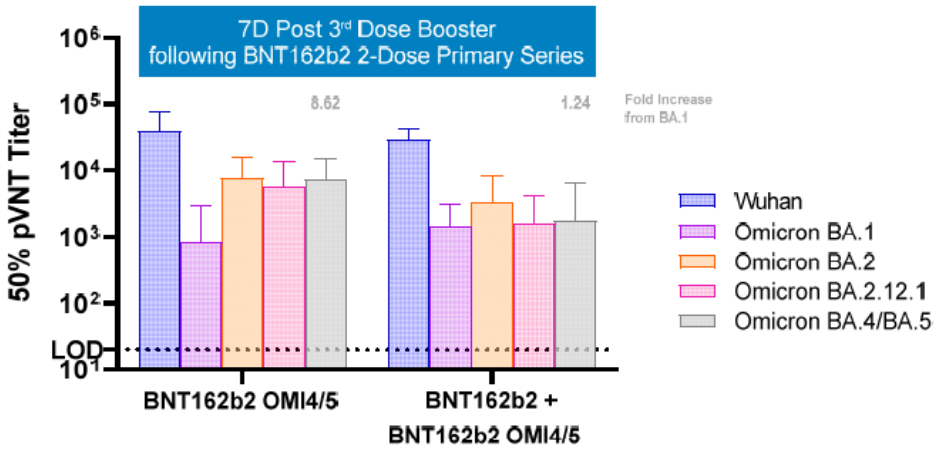


BNT162b2-experienced Balb/c mice (n=15/group; received 2 doses of 0.5 ug BNT162b2 at Days 0 and 21) were immunized IM with 0.5 µg of the indicated LNP-formulated modRNA vaccine as a 3rd dose booster 1 month after the prior BNT162b2 dose. Sera collected at 1 month post dose 3 were tested for SARS CoV-2 pseudovirus 50% neutralization titers (pVNT) against Wuhan reference strain, Beta, Delta, Omicron BA.1 and BA.4/BA.5. Bars indicate the GMT for each group and strain and vertical whiskers within each bar indicate the 95% confidence interval. The GMR of Omicron BA.4/BA.5 GMTs compared to Omicron BA.1 GMTs for each vaccine group are indicated in grey text above the grey bar. LOD, limit of detection.

Omicron BA.4/BA.5 Variant-modified Vaccine

The monovalent or bivalent Omicron BA.4/BA.5 variant-modified vaccines were tested as a two dose primary series in naïve Balb/c mice and as a 3rd dose booster in BNT162b2-experienced Balb/c mice. Sera were collected 1 month following a two dose primary series (vaccinations on Day 0 and Day 21) of the BNT162b2 prototype vaccine and 7 days after a 3rd dose of either a monovalent or bivalent BA.4/BA.4 variant-modified vaccine. Sera were tested in the non-validated SARS-CoV-2 pseudovirus neutralization assay. Initial immunization of a two dose primary series of BNT162b2 at 0.5 µg dose level to establish the cohort of BNT162b2-experienced mice (Groups 4 and 5) showed a high neutralizing antibody response against the Wuhan strain and substantially lower neutralizing titers against Omicron BA.1, BA.2, and BA.4/BA.5. In contrast to the clear reduction in BA.4/BA.5 neutralization observed in prior studies following a 3rd dose booster with the BA.1-modified vaccine or BNT162b2 prototype vaccine, a BA.4/BA.5 booster elicited substantially higher BA.4/BA.5 neutralizing titers and a more consistent response across Omicron sublineages (Figure 2.4.2-7).

Figure 2.4.2-7. BNT162b2 BA.4/BA.5 Vaccine Third Dose/Booster in BNT162b2-Experienced Balb/c Mice



BNT162b2-experienced Balb/c mice (n=10/group; received 2 doses of 0.5 ug BNT162b2 at Days 0 and 21) were immunized IM with 0.5 µg of the indicated LNP-formulated modRNA vaccine as a 3rd dose booster 1 month after the prior BNT162b2 dose. Sera collected at 1 month post dose 3 were tested for SARS CoV-2 pseudovirus 50% neutralization titers (pVNT) against the Wuhan reference strain (blue) and Omicron BA.1 (purple), BA.2 (orange), BA.2.12.1 (pink), and BA.4/BA.5 (grey) variants of concern. Bars indicate the GMT for each group and strain and vertical whiskers within each bar indicate the 95% confidence interval. The GMR of Omicron BA.4/BA.5 GMTs compared to Omicron BA.1 GMTs for each vaccine group are indicated in grey text above the grey bar. LOD, limit of detection.

4.3 Discussion on non-clinical aspects

The mouse immunogenicity studies performed by the MAH are of an explorative nature. They are not considered pivotal for this variation but give support to that the BA4/BA5 bivalent vaccine is likely to induce a higher antibody response to BA5 than the BA1 bivalent vaccine. Most importantly however, the approval of a BA4/BA5 vaccine should primarily be based on the scientific reasoning that a vaccine most similar to the currently dominating virus strain would be the best option for boosting the immune response.

Data are presented with variant-modified vaccines carrying Beta, Omicron BA1 and Omicron BA4/BA5. The data shows in all cases a robust neutralizing antibody response to the variant matched to the vaccine. Of particular importance for this submission were the findings after boosting with the bivalent BA1 vaccine. Similar to clinical data there was a stronger response to BA1 than to BA4/BA5. With the BA4/BA5 bivalent vaccine a balanced response to the different Omicron variants tested was observed with essentially a similar response to BA1 and BA4/BA5.

There are some limitations to these data. The comparison between the BA1 bivalent vaccine and the BA4/BA5 was not made within a study but is based on a cross-study comparison. However, the similar protocol for the studies with similar time intervals between primary series and booster dose and the same assay for neutralizing antibodies give some reassurance that the comparison is valid. While extrapolation from studies in experimental animals to the human situation always should be made with caution, in this case the study is focused on the antibody repertoire generated after immunisation. It is reasonable to believe that the selection of B-cells and the affinity maturation that is generated by somatic mutations in the IgG variable genes is a mechanism that is likely to be acting similarly, irrespective of species.

4.4 Conclusions on the non-clinical aspects

The CHMP is of the opinion that the non-clinical immunogenicity data are supporting that a BA4/BA5 bivalent vaccine may give a stronger immune response to BA5 than the BA1 bivalent vaccine.

5. Clinical aspects

5.1 Clinical efficacy

No new clinical studies concerning efficacy or immunogenicity were included in the current application. Efficacy is extrapolated from the original approval (Comirnaty) and approval of another bivalent variant-adapted vaccine (Comirnaty Original/Omicron BA.1 (15/15) micrograms/dose).

Efficacy of primary and booster doses of the original Comirnaty have been demonstrated in clinical efficacy studies in subjects from 12 years of age. In addition, immunogenicity data support the efficacy of a bivalent original/omicron BA.1 vaccine, which has been approved from 12 years of age recently. The bivalent Comirnaty Original/Omicron BA.1 vaccine induced superior antibody titres to BA.1 compared to the original Comirnaty, and non-inferior response to the Wuhan strain.

Therefore, the CHMP has agreed that it can be assumed that a bivalent original /omicron BA.5 will induce superior antibody responses to omicron BA.5 and non-inferior responses to the original strain, compared to the original vaccine.

Immunogenicity data to confirm this assumption are expected post-approval.

In addition, pre-clinical data support that the BA.5 variant-adapted mRNA can induce antibodies against omicron BA.5 (see section 2.3).

The CHMP considers that the following measures are considered necessary to address issues related to efficacy: the delivery of immunogenicity and safety data from study C4591044 (see section 8).

5.2 Clinical safety

There are no human reactogenicity or safety data for Original/BA.5. Rather, the inference of acceptable safety is based on extrapolation from the several different variant vaccines that have been studied.

Apart from the very extensive safety database for Comirnaty Original, the following data are considered pertinent to the extrapolation of safety.

5.2.1 Studies C4591031 Substudy D and E, C4591001

- **Original/BA.1 15/15 µg - C4591031 substudy E**

Methods

In this randomized, observer-blinded study 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 was evaluated.

The median time from dose 3 to study vaccination was 6,3 months (range 5-13 months). A majority (89%) had a duration of follow up of ≥1-<2 months after administration of the booster dose. This

interim safety data from 1841 subjects >55 years of age has been evaluated in EMEA/H/C/005735/II/0140. No data from subjects <55 years of age have been presented yet. The study was conducted in US. The reactogenicity data is summarized below.

Reactogenicity

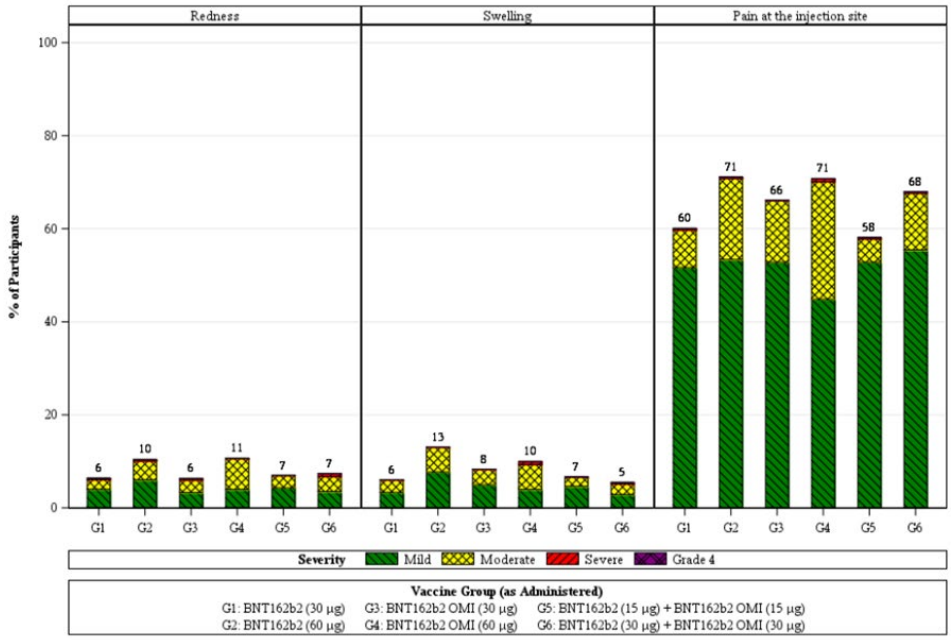
Local reactions

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 1. 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

Systemic reactions

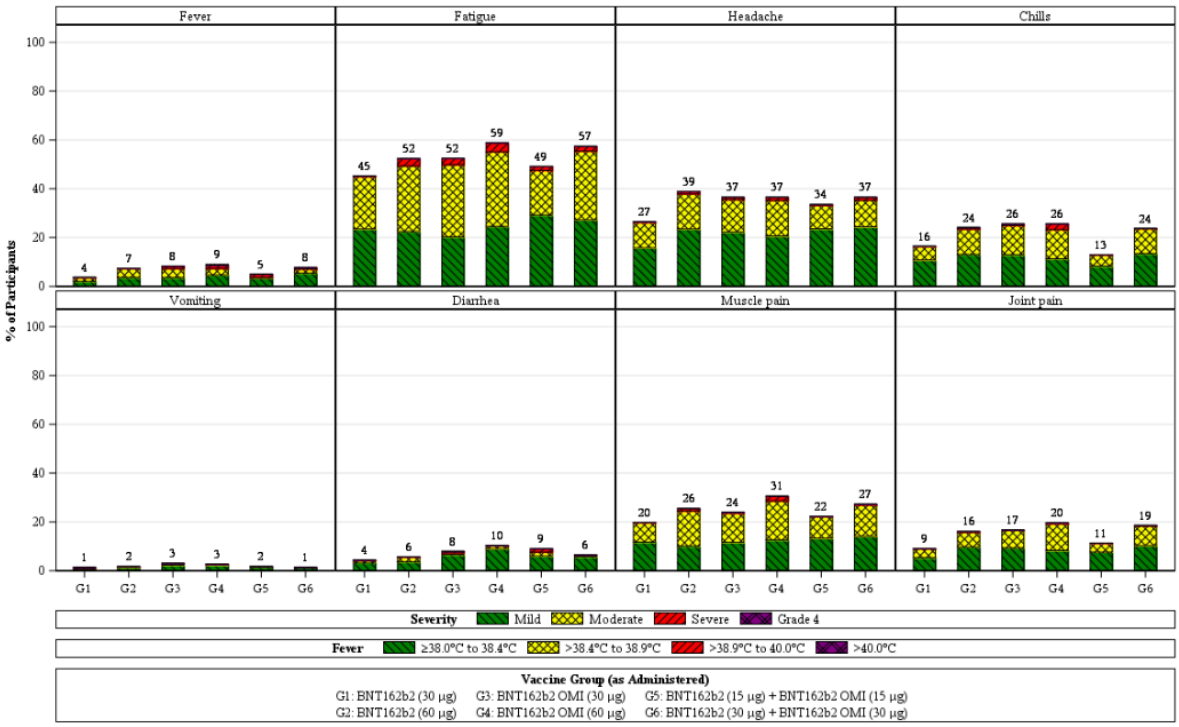
Fatigue was the most frequently reported systemic event, followed by headache, and less frequently chills, muscle and joint pain (Figure 2). Most systemic events were mild or moderate in severity.

Severe events were relatively more frequent in the BNT162b2 OMI 60 µg group. Overall, across all groups, severe events after study vaccination included fatigue (2.2%), headache (0.9%), chills (0.6%), muscle pain (0.6%), diarrhoea (0.3%) and joint pain (0.2%). No Grade 4 systemic events were reported in any vaccine groups evaluated.

Fever >38.9 °C to 40.0 °C was reported by 3 and 4 participants in the BNT162b2 OMI 30 µg and 60 µg groups, respectively: 4 and 2 participants in the BNT162b2 + BNT162b2 OMI 30 µg and 60 µg groups, respectively. Fever >40.0 °C was reported by 1 participant in the BNT162b2 60 µg group.

Antipyretic or pain medication were used at similar frequency for the subject that received Original/BA.1 15/15µg (29%) as for the subject that received Original 30µg (27%). A slightly higher frequency was noted for the subject that received the Original/BA.1 30/30µg vaccine (35%).

Figure 2. Participants Reporting Systematic 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

Adverse Events

Table 1. 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: /nda2_ube/C4591031_E_1MINEXP_EUA/adae_091_exp_cut

Many AEs were consistent with reactogenicity events that were reported as AEs (eg, injection site pain, diarrhoea, and pyrexia). There were no reported events of myocarditis or pericarditis (protocol-defined AESIs).

Overall, these data indicate a trend to somewhat higher reactogenicity when BA.1 is part of the vaccine, compared to Original. However, neither the differences in total frequency of reactions, nor of events classified as severe, is deemed clinically meaningful.

- **BA.1- C4591031 Substudy D**

Methods

In this substudy, 640 subjects aged 18-55 years were randomized 1:1 to either receive Original 30µg or BA.1 30µg as a fourth dose administered at least 3 months (median 4 months) after dose 3. The majority of the included subjects was >30 years of age and only 13% (n=84) were 18-30 years old. All subjects, except one, had at the cut-off date 11 Mars 2022 a duration of follow-up of ≥1-<2 months after administration of the booster dose. The study was conducted in US.

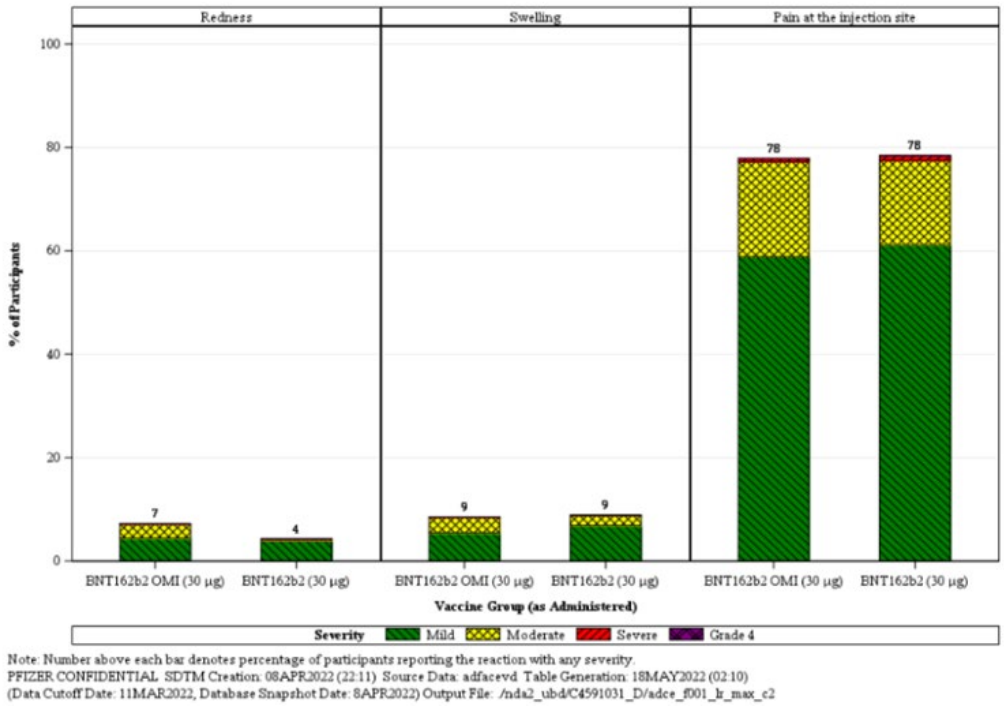
The interim data has been evaluated in EMEA/H/C/005735/II/0140. The reactogenicity data is summarized below.

Reactogenicity

Local reactions

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

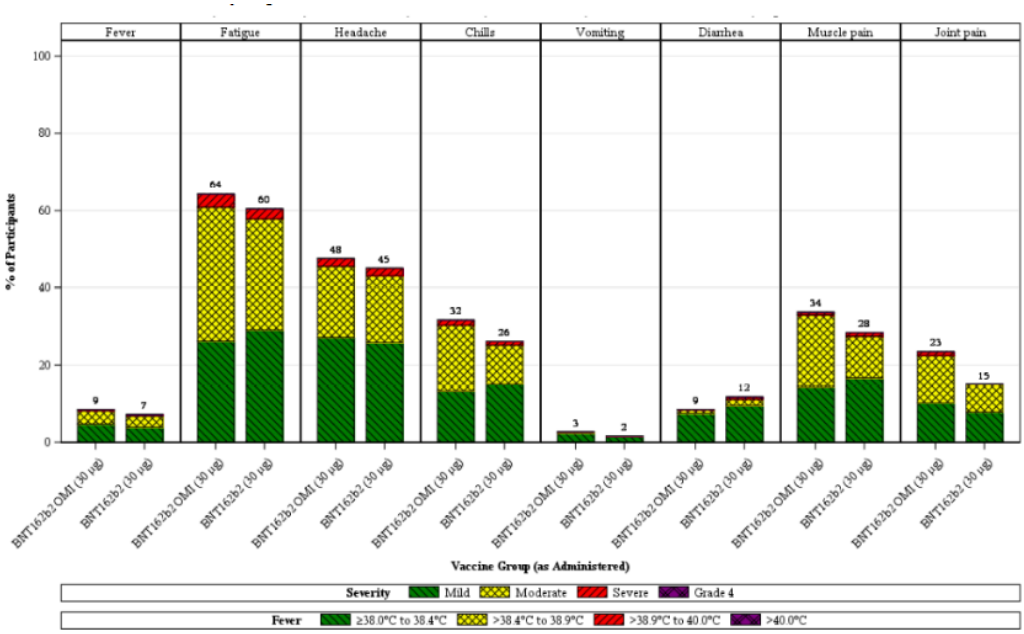


Systemic reactions

The proportion of severe systemic events reported was low, and similar between the vaccine groups. In both the BNT162b2 OMI and BNT162b2 groups, the most frequently reported severe systemic events were fatigue (3.4% and 2.6% of participants, respectively) followed by headache (2.0% and 2.0% of participants, respectively). 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 4. Participants Reporting Systematic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Cohort 2 – Safety Population



Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 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

Adverse events

For the AEs reported, most 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 BNT162b2 OMI group versus BNT162b2 group:

1. general disorders and administration site conditions: 9 (2.9%) vs 0
2. musculoskeletal and connective tissue disorders: 5 (1.6%) vs 2 (0.6%)
3. nervous system disorders: 4 (1.3%) vs 1 (0.3%)
4. gastrointestinal disorders: 0 vs 2 (0.6%)

From first study (Dose 4) vaccination to 1 month after Dose 4, the frequency of severe AEs was 1.3% for the BNT162b2 OMI group, and 0.6% for BNT162b2 groups. In the BNT162b2 OMI group, all severe events were reactogenicity events: fatigue, chills, arthralgia, and headache. No life-threatening (i.e., Grade 4) AEs were reported after Dose 4 in either vaccine group.

Besides AEs that reflect reactogenicity events (including fatigue in 5 participants in the BNT162b2 OMI group), AEs reflecting lymphadenopathy included lymphadenopathy in 1 participant (0.3%) and 3 participants (0.9%) in the BNT162b2 OMI and BNT162b2 groups, respectively, and axillary pain (0.3%) in 1 participant in the BNT162b2 OMI group; all other AEs were reported in ≤3 participants across vaccine groups. Lymphadenopathy has previously been identified as a reaction caused by BNT162b2.

There were no cases of myocarditis reported.

- **BNT162b2 SA (beta) - C4591001**

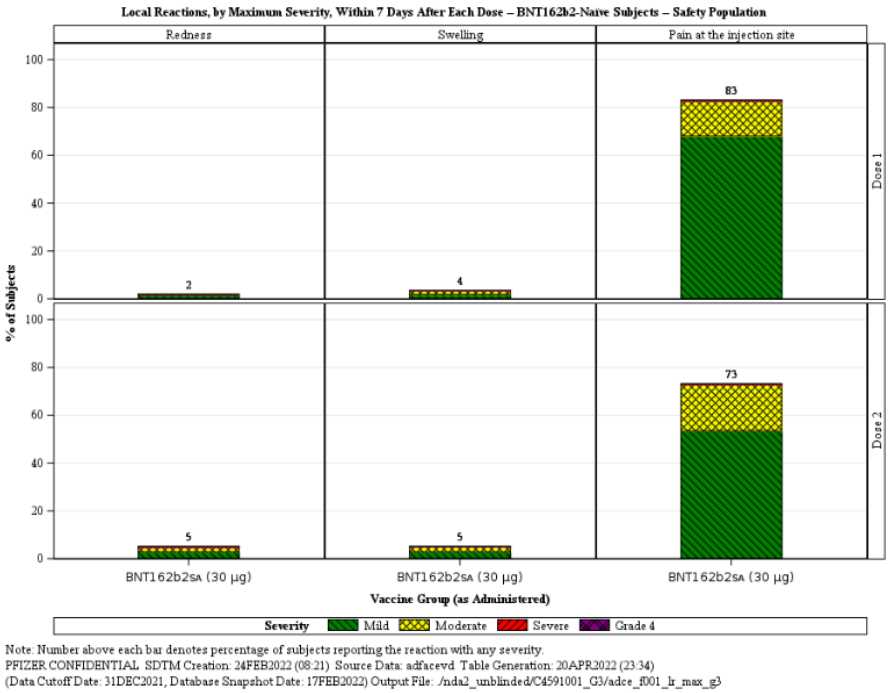
Primary vaccination-naïve population

In total, 333 subjects aged 18-55 years (median 36 years) received BNT162b2 SA 30µg as a primary vaccination. Most of the subjects (93%) had a follow-up time of ≥8-<10 months at the cut-off date 22 Nov 20211. The study was conducted in US. The reactogenicity is summarized below.

Local reactions

Pain at the injection site was the most frequently reported local reaction, as illustrated in the table below. After the first and second dose, most local reactions were mild or moderate in severity. Severe local reactions were reported infrequently, and no Grade 4 local reactions were reported. Median onset for all local reactions after either dose of BNT162b2SA 30 µg was 1-2 days.

Figure 5. Subjects Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 3 – BNT162b2-Naïve Subjects – Safety Population



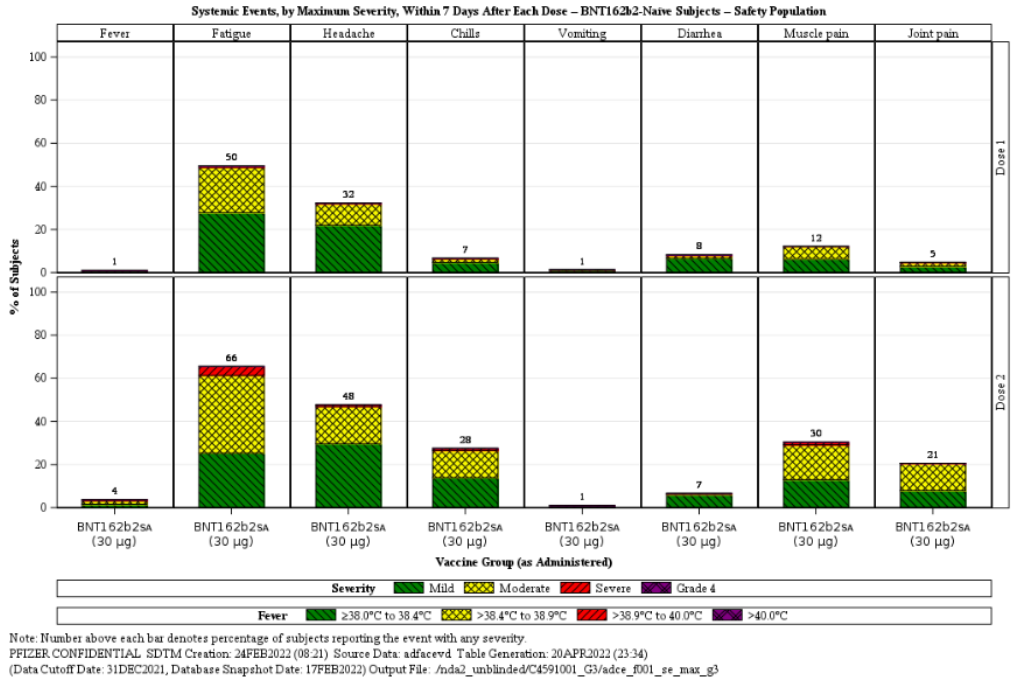
Systemic reactions

Use of antipyretic/pain medication was greater after Dose 2 of BNT162b2SA 30 µg compared with Dose 1 (31.6% and 18.8%, respectively), showing the same pattern of higher reactogenicity for dose 2, as was seen for Comirnaty Original.

Most systemic events were mild or moderate in severity, and severe systemic events were reported infrequently (≤4.1%) after any dose.

Median onset for all systemic events after either dose was Day 1.0 to Day 4.5 (Day 1 was the day of vaccination). Systemic events resolved after each dose with a median duration of 1-2 days.

Figure 6. Subjects Reporting Systematic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 3 – BNT162b2-Naïve Subjects – Safety Population



Adverse events

From Dose 1 to 1 month after Dose 2 of BNT162b2SA 30 µg, the frequency of participants with any AE was 46 (14.2%).

The most frequently reported AE from Dose 1 to 1 month after Dose 2 of BNT162b2SA 30 µg was fatigue, in 10/324 participants (3.1%)). Most other AEs reported during this period reflect reactogenicity events reported by the investigator as AEs.

Lymphadenopathy was reported in 2/324 participants (0.6%) from Dose 1 to 6 months after Dose 2. Both events were assessed by the investigator as related to study intervention, and both events recovered/resolved within 1 week of onset.

One participant reported an AE of iritis on the second day from Dose 1 of BNT162b2SA 30 µg, which was assessed by the investigator as related to study intervention, and the event lasted for 23 days.

One participant reported an AE of type 1 diabetes mellitus on the 11th day from Dose 2 of BNT162b2SA 30 µg: A participant with a normal BMI in the 25 to 34 years age group reported two AEs of hyperglycaemia and diabetes mellitus type 1 with onset 11 days post-Dose 2 of BNT162b2SA 30 µg. The participant had no recorded past medical history or positive family history of diabetes. The diagnosis as confirmed by the site was made by an endocrinologist based on a GAD65 level of 60.4 and a c-peptide of 0.5. The source documentation stated a diagnosis of diabetes mellitus type 1.5, however the reported term reported in the clinical database is diabetes mellitus type 1. The investigator did not consider the event to be related to study intervention.

One participant reported an AE of diabetes mellitus 103 days from Dose 2 BNT162b2SA 30 µg. A participant with an overweight (almost obese) BMI in the 45 to 54 years age group reported an AE of diabetes mellitus 103 days post-Dose 2 of BNT162b2SA 30 µg. The participant had no past medical history of diabetes reported, however the investigator considered the participant's BMI and positive family history of diabetes as predisposing factors and confirmed that the diagnosis was made

incidentally on a routine annual check-up and there were no symptoms of diabetes mellitus reported. The event was considered not related to study intervention by the investigator.

There were no cases of myocarditis reported.

One booster dose with either BNT162b2 or BNT162b2 SA

In total, 625 subjects aged 19-62 years (median 43 years) that had previously received BNT162b2 30µg as primary vaccination, were randomized to either receive one booster dose of BNT162b2 30µg (n=312) or BNT162b2 SA 30µg (n=313). Reactogenicity data is available for BNT162b2 30µg (n=289) and BNT162b2 SA 30µg (n=298).

The majority received their booster dose ≥6 months after dose 2. Most of the subjects (97%) had a follow-up time of ≥8 months at the cut-off date 22 Nov 2021.

The study was conducted in US.

Local reactions

After Dose 3, most local reactions were mild or moderate in severity. Severe local reactions were reported infrequently. No Grade 4 local reactions were reported in either group. Median onset for all local reactions after Dose 3 was Day 1-2. (Day 1 was the day of vaccination) and resolved with a median duration of 1-2 days.

Figure 7. Subjects Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose (30µg) – Booster Safety Population

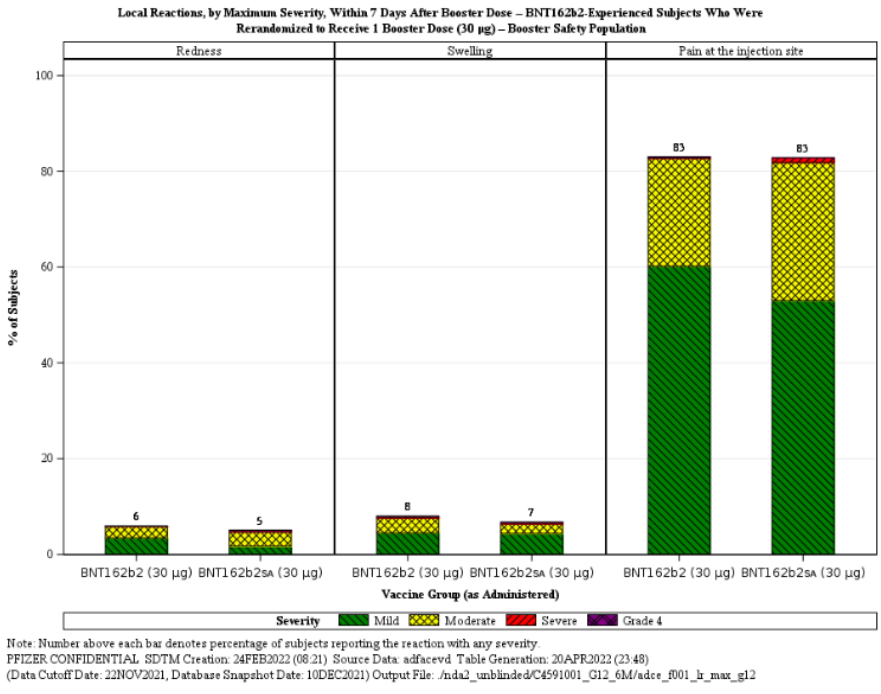


Table 2. Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Eperienced Subjects Who Were Rerandomized to Receive 1 Booster Dose (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg)			BNT162b2$_{SA}$ (30 µg)		
Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
Redness[d]						
Any	289	17 (5.9)	(3.5, 9.3)	298	15 (5.0)	(2.8, 8.2)
Mild	289	10 (3.5)	(1.7, 6.3)	298	5 (1.7)	(0.5, 3.9)
Moderate	289	7 (2.4)	(1.0, 4.9)	298	9 (3.0)	(1.4, 5.7)
Severe	289	0	(0.0, 1.3)	298	1 (0.3)	(0.0, 1.9)
Grade 4	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
Swelling[d]						
Any	289	23 (8.0)	(5.1, 11.7)	298	20 (6.7)	(4.1, 10.2)
Mild	289	13 (4.5)	(2.4, 7.6)	298	13 (4.4)	(2.3, 7.3)
Moderate	289	9 (3.1)	(1.4, 5.8)	298	6 (2.0)	(0.7, 4.3)
Severe	289	1 (0.3)	(0.0, 1.9)	298	1 (0.3)	(0.0, 1.9)
Grade 4	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
Pain at the injection site[e]						
Any	289	240 (83.0)	(78.2, 87.2)	298	247 (82.9)	(78.1, 87.0)
Mild	289	174 (60.2)	(54.3, 65.9)	298	158 (53.0)	(47.2, 58.8)
Moderate	289	65 (22.5)	(17.8, 27.7)	298	86 (28.9)	(23.8, 34.4)
Severe	289	1 (0.3)	(0.0, 1.9)	298	3 (1.0)	(0.2, 2.9)
Grade 4	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
Any local reaction[f]	289	240 (83.0)	(78.2, 87.2)	298	249 (83.6)	(78.9, 87.6)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 through Day 7 after the booster dose.
Note: Grade 4 reactions were classified by the investigator or medically qualified person.
a. N = number of subjects reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of subjects 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: 24FEB2022 (08:21) Source Data: adfacevd Table Generation: 20APR2022 (23:48)
(Data Cutoff Date: 22NOV2021, Database Snapshot Date: 10DEC2021) Output File:

Systemic reactions

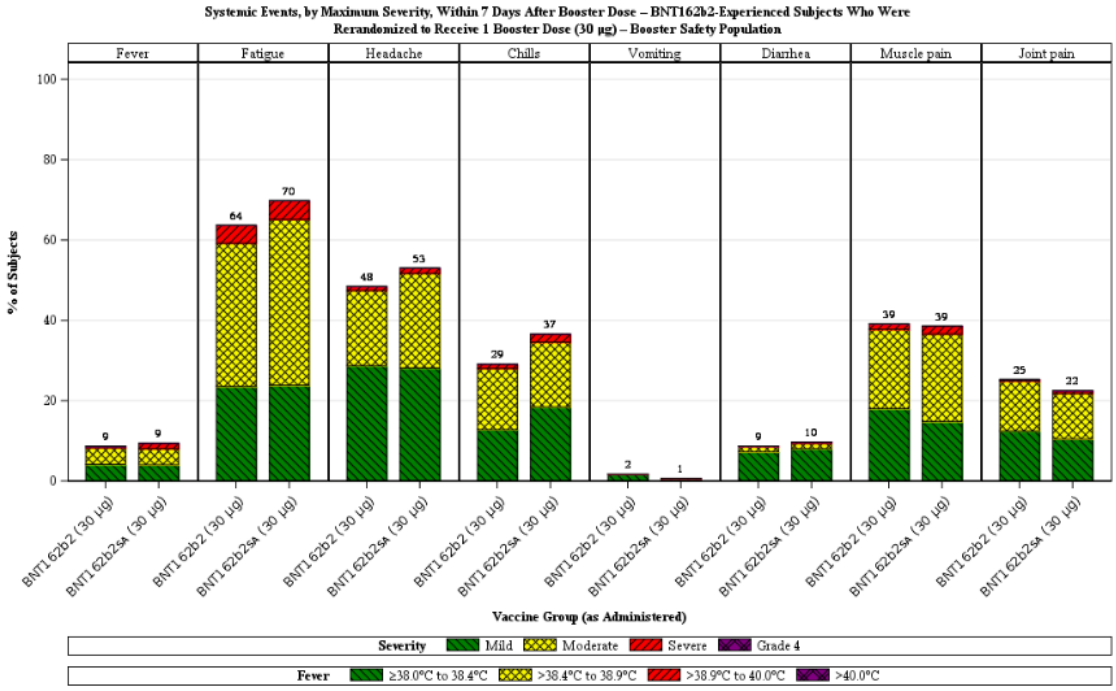
After Dose 3, use of antipyretic/pain medication was similar in the BNT162b2 and BNT162b2SA groups (46.7% vs 45.3%, respectively).

Most systemic events were mild or moderate in severity. Severe systemic events were reported infrequently, in ≤2.0% of participants for all systemic events except for severe fatigue (≤4.7%). One participant (0.3%) in the BNT162b2 group and 4 participants (1.3%) in the BNT162b2SA group reported a fever of >38.9°C to 40°C, with oral temperatures that returned to normal by the end of the 7-day reporting period (Appendix 16.2.7.3.1).

No Grade 4 systemic events were reported.

In both groups, the median onset for all systemic events after Dose 3 was Day 2-4, and systemic events resolved within a median duration of 1-2 days.

Figure 8. Subjects Reporting Systematic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose (30µg) – Booster Safety Population



Note: Number above each bar denotes percentage of subjects reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 24FEB2022 (08:21) Source Data: adfacevd Table Generation: 20APR2022 (23:48)
(Data Cutoff Date: 22NOV2021, Database Snapshot Date: 10DEC2021) Output File: /nda2_unblinded/C4591001_G12_6M/adce_f001_se_max_g12

Table 3. Systematic Events, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Eperienced Subjects Who Were Rerandomized to Receive 1 Booster Dose (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg)			BNT162b2$_{SA}$ (30 µg)		
Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
Fever						
≥38.0°C	289	25 (8.7)	(5.7, 12.5)	298	28 (9.4)	(6.3, 13.3)
38.0°C to 38.4°C	289	12 (4.2)	(2.2, 7.1)	298	12 (4.0)	(2.1, 6.9)
>38.4°C to 38.9°C	289	12 (4.2)	(2.2, 7.1)	298	12 (4.0)	(2.1, 6.9)
>38.9°C to 40.0°C	289	1 (0.3)	(0.0, 1.9)	298	4 (1.3)	(0.4, 3.4)
>40.0°C	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
Fatigue[d]						
Any	289	184 (63.7)	(57.8, 69.2)	298	208 (69.8)	(64.2, 75.0)
Mild	289	68 (23.5)	(18.8, 28.9)	298	71 (23.8)	(19.1, 29.1)
Moderate	289	103 (35.6)	(30.1, 41.5)	298	123 (41.3)	(35.6, 47.1)
Severe	289	13 (4.5)	(2.4, 7.6)	298	14 (4.7)	(2.6, 7.8)
Grade 4	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
Headache[d]						
Any	289	140 (48.4)	(42.5, 54.4)	298	158 (53.0)	(47.2, 58.8)
Mild	289	83 (28.7)	(23.6, 34.3)	298	84 (28.2)	(23.2, 33.7)
Moderate	289	54 (18.7)	(14.4, 23.7)	298	70 (23.5)	(18.8, 28.7)
Severe	289	3 (1.0)	(0.2, 3.0)	298	4 (1.3)	(0.4, 3.4)
Grade 4	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
Chills[d]						
Any	289	84 (29.1)	(23.9, 34.7)	298	109 (36.6)	(31.1, 42.3)
Mild	289	37 (12.8)	(9.2, 17.2)	298	55 (18.5)	(14.2, 23.3)
Moderate	289	44 (15.2)	(11.3, 19.9)	298	48 (16.1)	(12.1, 20.8)
Severe	289	3 (1.0)	(0.2, 3.0)	298	6 (2.0)	(0.7, 4.3)
Grade 4	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
Vomiting[e]						
Any	289	5 (1.7)	(0.6, 4.0)	298	2 (0.7)	(0.1, 2.4)
Mild	289	5 (1.7)	(0.6, 4.0)	298	2 (0.7)	(0.1, 2.4)
Moderate	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
Severe	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
Grade 4	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
Diarrhea[f]						

Any	289	25 (8.7)	(5.7, 12.5)	298	29 (9.7)	(6.6, 13.7)
Mild	289	21 (7.3)	(4.6, 10.9)	298	24 (8.1)	(5.2, 11.7)
Moderate	289	4 (1.4)	(0.4, 3.5)	298	4 (1.3)	(0.4, 3.4)
Severe	289	0	(0.0, 1.3)	298	1 (0.3)	(0.0, 1.9)
Grade 4	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
New or worsened muscle pain[d]						
Any	289	113 (39.1)	(33.4, 45.0)	298	115 (38.6)	(33.0, 44.4)
Mild	289	52 (18.0)	(13.7, 22.9)	298	44 (14.8)	(10.9, 19.3)
Moderate	289	57 (19.7)	(15.3, 24.8)	298	65 (21.8)	(17.3, 26.9)
Severe	289	4 (1.4)	(0.4, 3.5)	298	6 (2.0)	(0.7, 4.3)
Grade 4	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
New or worsened joint pain[d]						
Any	289	73 (25.3)	(20.4, 30.7)	298	67 (22.5)	(17.9, 27.7)
Mild	289	36 (12.5)	(8.9, 16.8)	298	31 (10.4)	(7.2, 14.4)
Moderate	289	36 (12.5)	(8.9, 16.8)	298	34 (11.4)	(8.0, 15.6)
Severe	289	1 (0.3)	(0.0, 1.9)	298	2 (0.7)	(0.1, 2.4)
Grade 4	289	0	(0.0, 1.3)	298	0	(0.0, 1.2)
Any systemic event[g]	289	223 (77.2)	(71.9, 81.9)	298	234 (78.5)	(73.4, 83.0)
Use of antipyretic or pain medication[h]	289	135 (46.7)	(40.8, 52.6)	298	135 (45.3)	(39.6, 51.1)

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 booster dose. Grade 4 events were classified by the investigator or medically qualified person.
a. N = number of subjects reporting at least 1 yes or no response for the specified event after the specified dose.
b. n = Number of subjects 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: 24FEB2022 (08:21) Source Data: adfacevd Table Generation: 20APR2022 (23:48)
(Data Cutoff Date: 22NOV2021, Database Snapshot Date: 10DEC2021) Output File:

Adverse events

From Dose 3 to 1 month after Dose 3, 46 (15.0%) and 34 (10.8%) BNT162b2-experienced participants who were rerandomized and received one 30-µg booster dose reported at least 1 AE in the BNT162b2 and BNT162b2SA groups, respectively, of which 25 (8.2%) and 23 (7.3%) were assessed by the investigator as related to study intervention.

One participant in the BNT162b2SA group reported an SAE of deep vein thrombosis. No AEs leading to withdrawal or deaths were reported. AEs from Dose 3 to 6 months after Dose 3 were generally similar in the BNT162b2 and BNT162b2SA groups. AEs were reported in 51 (16.7%) participants in the BNT162b2 group and 38 (12.1%) participants in the BNT162b2SA group,

In the BNT162b2 group, the most frequently reported AE from Dose 3 to 1 month after Dose 3 was lymphadenopathy (16 [5.2%] participants). In the BNT162b2SA group, injection site pain, headache, and lymphadenopathy were most frequently reported (6 [1.9%] participants each). Most other AEs reported during this period reflect reactogenicity events reported by the investigator as AEs. No immediate events were reported within 30 minutes after Dose 3.

One or two booster doses

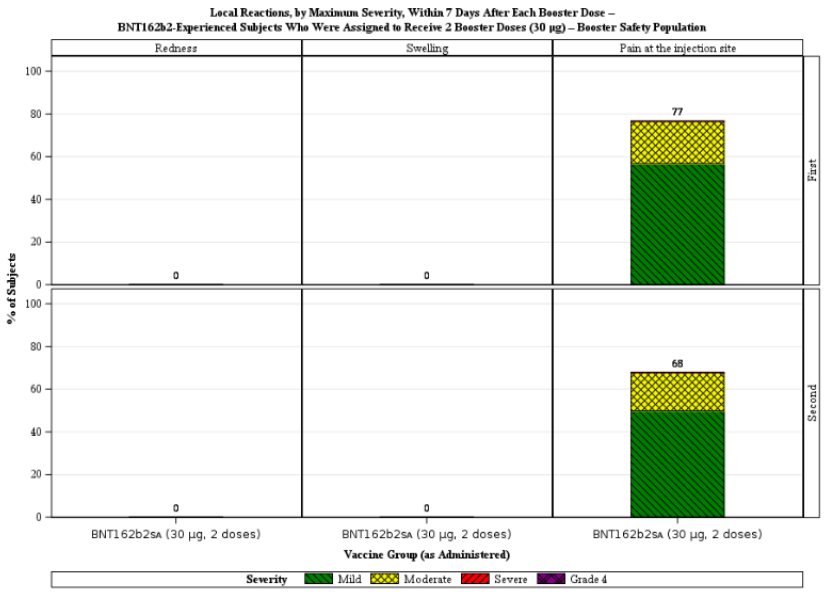
Thirty subjects aged 22-55 years (median 44 years) that previously have received a primary vaccination with BNT162b2 30µg received BNT162b2 SA 30µg as booster dose at least 6 months after dose 2. All subjects received the first booster dose, and 28 subjects received the second booster dose. The majority of the subjects (90%) had a follow-up time of ≥6-<8 months at the cut-off date 22 Nov 20211.

The study was conducted in the US.

Local reactions

Pain at the injection site was all mild or moderate in severity. Median onset for pain at the injection site after Dose 3 and Dose 4 was Day 1.0 (Day 1 was the day of vaccination) and resolved with a median duration of 2-3 days.

Figure 9. Subjects Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Assigned to Receive 2 Booster Doses (30 µg) – Safety Population



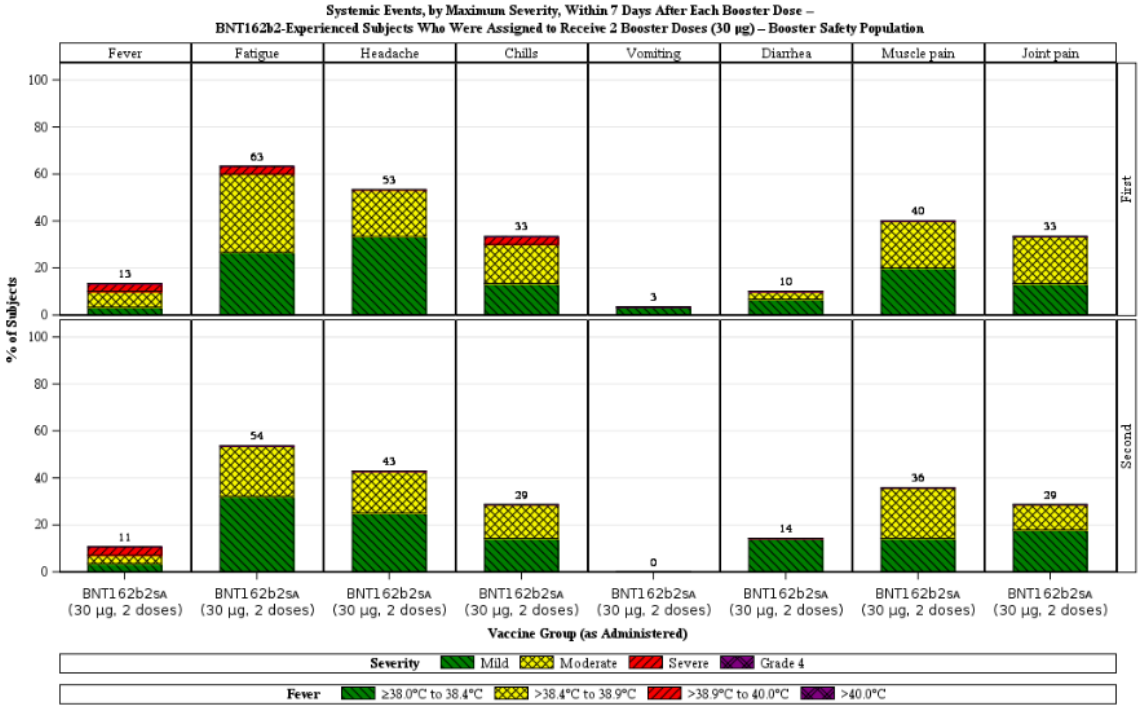
Note: Number above each bar denotes percentage of subjects reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 24FEB2022 (08:21) Source Data: adfacevd Table Generation: 20APR2022 (23:48)
(Data Cutoff Date: 22NOV2021, Database Snapshot Date: 10DEC2021) Output File: /nda2_unblinded/C4591001_G12_6M/adce_f001_lr_max_g0

Systemic reactions

Use of antipyretic/pain medication was similar after Dose 3 and Dose 4 of BNT162b2SA 30 µg (50.0% vs 46.4%, respectively).

Most systemic events were mild or moderate in severity. Severe systemic events were reported infrequently (1 participant for any systemic event). One participant reported a fever of >38.9°C to 40°C after the first and second booster dose of BNT162b2SA 30 µg, with oral temperatures that returned to normal by the end of the first booster 7-day reporting period. No Grade 4 systemic events were reported. The median onset for all systemic events after Dose 3 and Dose 4 was Day 2 (Day 1 was the day of vaccination), and systemic events resolved within a median duration of 1-2 days.

Figure 10. Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Assigned to Receive 2 Booster Doses (30 µg) – Safety Population



Note: Number above each bar denotes percentage of subjects reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 24FEB2022 (08:21) Source Data: adfacevd Table Generation: 20APR2022 (23:48)
(Data Cutoff Date: 22NOV2021, Database Snapshot Date: 10DEC2021) Output File: /nda2_unblinded/C4591001_G12_6M/adce_f001_se_max_g0

Adverse events

From the first booster (Dose 3) to 1 month after the second booster (Dose 4), 6 (20.0%) BNT162b2-experienced participants who were assigned to receive two 30-µg booster doses reported at least 1 AE, of which 3 (10.0%) participants had AE(s) assessed by the investigator as related to study intervention.

Two participants (6.7%) each reported an AE of lymphadenopathy or an AE of arthralgia from Dose 3 to 1 month after Dose 4. No immediate AEs were reported after Dose 3 or Dose 4. No additional participants reported AEs from Dose 3 to approximately 5 months after Dose 4. Both events of lymphadenopathy and reactogenicity events were assessed by the investigator as related to study intervention. One participant had a severe AE (also an SAE) of appendicitis. No life-threatening AEs or deaths were reported.

There were 2 (6.7%) BNT162b2-experienced participants assigned to receive 2 booster doses who reported AEs leading to withdrawal from study intervention. One participant reported lymphadenopathy on the second day from Dose 3, which resolved approximately 1 week later, and 1 participant reported reactogenicity AEs after Dose 3 of chills, fatigue, injection site pain, arthralgia, and myalgia, which all resolved within 3 days after onset.

- **Safety Summary of Studies C4591001, C4591031 Substudy D and E**

In conclusion, the safety of studies C4591001, C4591031 Substudy D and E is summarised in the two tables below:

Table 4. Participants Reporting Local Reactions and Systematic Events Within 7 Days Post Dose 3 or Dose 4 of BNT162b2, Monovalent BNT162b2 OMI, Bivalent BNT162b2+BNT162b2 OMI or BNT162Bt$_{sa}$ at 30 µg Dose Level in Studies C4591001, Studies C4591031 Substudy D and C4591031 Substudy E

Events	C4591031 Substudy D[a] (18 to 55 Years)		C4591031 Substudy E[b] (>55 Years)			C4591001[c] (18 to 55 Years)	
	BNT162b2 OMI 30 µg	BNT162b2 30 µg	BNT162b2 30 µg	BNT162b2 OMI 30 µg	BNT162b2 + BNT162b2 OMI 30 µg	BNT162b2 30 µg	BNT162b2$_{SA}$ 30 µg
	Dose 4 (N=294)	Dose 4 (N=306)	Dose 4 (N=298)	Dose 4 (N=301)	Dose 4 (N=301)	Dose 3 (N=289)	Dose 3 (N=298)
Local reaction at injection site: Total (Severe)*							
Pain	77.9% (0.7%)	78.4% (1.0%)	60.1% (0.3%)	66.1% (0%)	58.1% (0.3%)	83.0% (0.3%)	82.9% (1.0%)
Swelling	8.5% (0%)	8.8% (0%)	6.0% (0%)	8.3% (0%)	6.6% (0%)	8.0% (0.3%)	6.7% (0.3%)
Redness	7.1% (0%)	4.2% (0%)	6.4% (0.3%)	6.3% (0.3%)	7.0% (0%)	5.9% (0%)	5.0% (0.3%)
Systemic events: Total (Severe)*							
Fatigue	64.3% (3.4%)	60.5% (2.6%)	45.3% (0.3%)	52.5% (2.7%)	49.2% (1.7%)	63.7% (4.5%)	69.8% (4.7%)
Headache	47.6% (2.0%)	45.1% (2.0%)	26.5% (0.3%)	36.5% (1.0%)	33.6% (0.3%)	48.4% (1.0%)	53.0% (1.3%)
Muscle pain	33.7% (0.7%)	28.4% (1.0%)	19.8% (0%)	23.9% (0.3%)	22.3% (0%)	39.1% (1.4%)	38.6% (2.0%)
Chills	31.6% (1.4%)	26.1%(1.0%)	16.4% (0%)	25.6% (0.7%)	13.0% (0%)	29.1% (1.0%)	36.6% (2.0%)
Joint pain	23.5% (1.0%)	15.0% (0%)	9.1% (0%)	16.6% (0%)	11.3% (0%)	25.3% (0.3%)	22.5% (0.7%)
Fever (≥38.0°C)	8.5% (0.3%)	7.2% (0.3%)	3.7% (0%)	8.3% (1.0%)	5.0% (1.3%)	8.7% (0.3%)	9.4% (1.3%)
Vomiting	2.7% (0%)	1.6% (0%)	1.3% (0%)	3.0% (0%)	1.7% (0%)	1.7% (0%)	0.7% (0%)
Diarrhea	8.5% (0%)	11.8% (0.7%)	4.4% (0%)	8.0% (0.7%)	9.0% (1.3%)	8.7% (0%)	9.7% (0.3%)
Use of Antipyretic or pain medication[d]	38.8%	39.5%	26.8%	34.9%	29.2%	46.7%	45.3%

a. BNT162b2-experienced participants (18 to 55 years of age) who received either BNT162b2 30 µg or BNT162b2 OMI 30 µg as a booster (Dose 4) approximately 3 to 6 months (90 to 180 days) after their last dose (Dose 3).
b. BNT162b2-experienced participants (>55 years of age) who received BNT162b2 30 µg or BNT162b2 OMI 30 µg or BNT162b2 + BNT162b2 OMI 30 µg as a booster dose (Dose 4) approximately 5 to 12 months after their last dose (Dose 3).
c. BNT162b2-experienced participants (18 to 55 years of age) who were randomized to receive a booster (Dose 3) dose of BNT162b2 30 µg or BNT162b2SA 30 µg approximately 6 months after their second dose of BNT162b2 30 µg (Dose 2).
d. Severity was not collected for use of antipyretic or pain medication.
* No Grade 4 events were reported.

Table 5. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 3 or Dose 4 to 1 Month After Dose 3 or Dose 4 of BNT162b2, Monovalent BNT162b2 OMI, Bivalent BNT162b2+BNT162b2 OMI or BNT162Bt$_{SA}$ at 30 µg Dose Level in Studies C4591001, Studies C4591031 Substudy D and C4591031 Substudy E

Adverse Events	C4591031 Substudy D[a]		C4591031 Substudy E[b]			C4591001[c]	
	BNT162b2 OMI 30 µg	BNT162b2 30 µg	BNT162b2 30 µg	BNT162b2 OMI 30 µg	BNT162b2 + BNT162b2 OMI 30 µg	BNT162b2 30 µg	BNT162b2$_{SA}$ 30 µg
	Dose 4 (N=315)	Dose 4 (N=325)	Dose 4 (N=305)	Dose 4 (N=307)	Dose 4 (N=305)	Dose 3 (N=306)	Dose 3 (N=315)
Any AE	18 (5.7%)	12 (3.7%)	18 (5.9%)	26 (8.5%)	19 (6.2%)	46 (15.0%)	34 (10.8%)
Related	10 (3.2%)	5 (1.5%)	4 (1.3%)	10 (3.3%)	7 (2.3%)	25 (8.2%)	23 (7.3%)
Severe	4 (1.3%)	2 (0.6%)	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Life-threatening	0	0	0	0	0	0	0
Any SAE	1 (0.3%)	1 (0.3%)	0	3 (1.0%)	1 (0.3%)	0	1 (0.3%)
Related	0	0	0	1 (0.3%)	0	0	0
Severe	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)
Life-threatening	0	0	0	0	0	0	0
Any nonserious AE	17 (5.4%)	12 (3.7%)	18 (5.9%)	24 (7.8%)	18 (5.9%)	46 (15.0%)	33 (10.5%)
Related	10 (3.2%)	5 (1.5%)	4 (1.3%)	10 (3.3%)	7 (2.3%)	25 (8.2%)	23 (7.3%)
Severe	4 (1/3%)	1 (0.3%)	0	0	0	1 (0.3%)	0
Life-threatening	0	0	0	0	0	0	0
Any AE leading to withdrawal	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0

a. BNT162b2-experienced participants (18 to 55 years of age) who received either BNT162b2 30 µg or BNT162b2 OMI 30 µg as a booster (Dose 4) approximately 3 to 6 months (90 to 180 days) after their last dose (Dose 3).

b. BNT162b2-experienced participants (>55 years of age) who received BNT162b2 30 µg or BNT162b2 OMI 30 µg or BNT162b2 + BNT162b2 OMI 30 µg as a booster dose (Dose 4) approximately 5 to 12 months after their last dose (Dose 3).

c. BNT162b2-experienced participants (18 to 55 years of age) who were randomized to receive a booster (Dose 3) dose of BNT162b2 30 µg or BNT162b2$_{SA}$ 30 µg approximately 6 months after their second dose of BNT162b2 30 µg (Dose 2).

5.2.2 Study BNT162 - monovalent delta and bivalent alpha/delta vaccine

Study BNT162-17 is an ongoing (Start date: 25 August 2021) Phase 2 study. The study consists of three parts, Part A, Part B, and Part C, and will evaluate the safety and immunogenicity of monovalent Delta-variant (BNT162b2 [B.1.617.2]) at 30 ug, and bivalent Alpha and Delta-variant (BNT162b2 [B.1.1.7 + B.1.617.2]) at 15ug + 15ug.

Safety data up to 1-month post-Dose (booster [Dose 3]) for cohort 1 and 4 of part A and B of the study for monovalent BNT162b2 (B.1.617.2) and bivalent BNT162b2 (B.1.1.7 + B.1.617.2) vaccine has only been presented.

Cohort 1: BNT162b2 (B.1.1.7 + B.1.617.2) – bivalent alpha/delta

A total of 370 participants were included in the safety population for Cohort 1: 21 participants (18 to 55 years of age) in Part A of the study and 349 participants (18 to 55 years of age: 222, 56 to 85 years of age: 127) in Part B of the study. A total of 9 participants discontinued from the study. Most frequent reason for discontinuation was 'lost to follow up' (n=4). No participants discontinued due to an AE.

Cohort 4: BNT162b2 (B.1.617.2) – monovalent delta

A total of 372 participants were included in the safety population for Cohort 4: 20 participants (18 to 55 years of age) in Part A of the study and 352 participants (18 to 55 years of age: 210, 56 to 85 years of age: 142) in Part B of the study. A total of 2 participants discontinued from the study. No participants discontinued due to an AE.

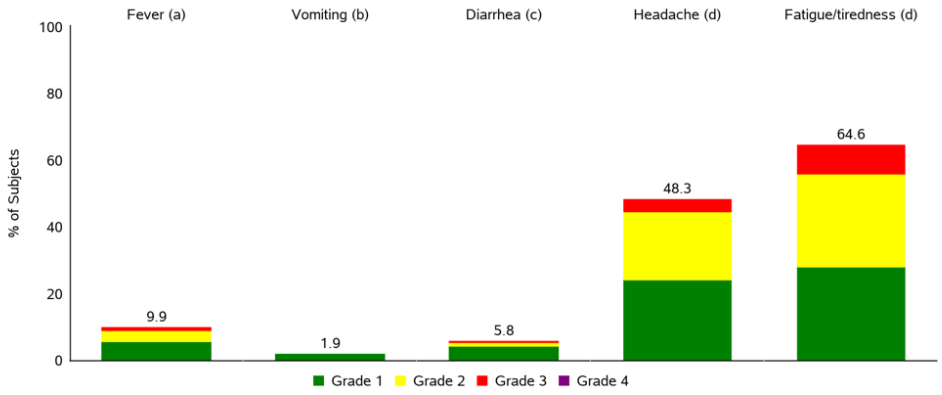
Results

	BNT 162-17 Part B cohort 1		BNT 162-17 Part B cohort 4	
	Alpha+Delta Dose 3		Delta Dose 3	
Age group	18-55	56-85	18-55	56-85
	N=220	N=121	N=206	N=140
	Any reported reacogenicity events %(severe events%)			
Local reaction at injection site				
Pain at injection site	78.2% (7.3%)	67.8%(0.8%)	81.1% (4.9%)	67.9% (0.7%)
Swelling	8.2% (1.4%)	14.9%(1.7%)	9.2% (0%)	7.9 %(1.4 %)
Redness	7.7%(2.3%)	14% (3.3%)	9.7% (1%)	7.1%(0%)
Systemic events				
Fatigue	69.1% (8.6%)	55.4% (5.8%)	68.9%(10.7%)	55%(5.0%)
Fever(≥38.0°C)	10.5% (1.4%)	7.4%(0%)	10.7% (1.5%)	8.6% (2.1%)
Headache	51.4% (3.6%)	38.8% (2.5%)	58.7% (4.4%)	40.7% (2.9%)
Muscle pain	36.8% (5.5%)	34.7% (1.7%)	42.2% (4.4%)	31.4%(2.1%)
Chills	27.7% (4.5%)	24.8% (1.7%)	36.9% (5.8%)	27.9%(5.0%)
Joint pain	27.7% (2.7%)	20.7% (0.8%)	25.7% (2.4%)	17.9% (1.4%)
Vomiting	1.8% (0%)	2.5% (0%)	1.5%(0%)	2.9% (0%)
Diarrhea	4.5% (0.5%)	7.4% (0%)	13.6% (1%)	7.9% (0%)
% taking antipyretic meds	Data not yet analyzed			

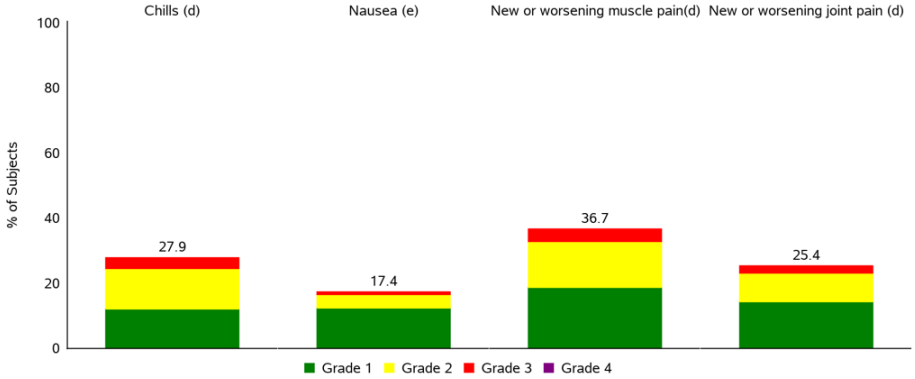
Note: No events of Local Tenderness and Nausea were populated to align with reactogenicity events as collected in study C4591031 and C4591001

Systemic reactions cohort 1

Figure 11. Systematic Events, by Maximum Severity, Within 7 Days After Vaccination – Cohort 1 Participants 18 to 85 Years of Age (Part A and Part B: Booster Dose, Dose 3) – BNT162b2 (B.1.1.7 + B.1.617.2) – Reactogenicity Set



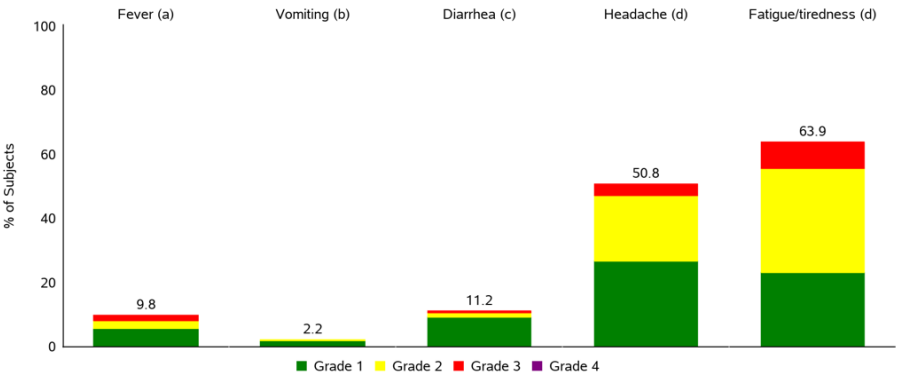
Systemic Events, by Maximum Severity, Within 7 Days of Study Vaccination- Cohort 1 Participants 18 to 85 Years of Age (Part A and Part B: Booster Dose, Dose 3) - BNT162b2 (B.1.1.7 + B.1.617.2) - Reactogenicity Set



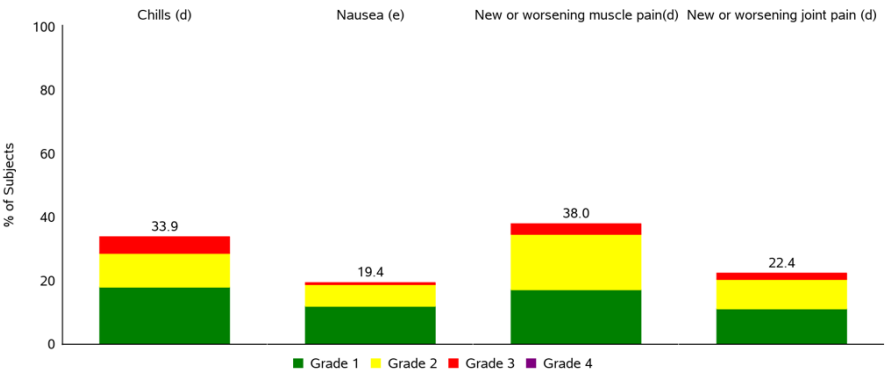
Date of Cut Off: Cohort 1 Part A:15Oct2021 and Cohort 1 Part B:04May2022. Notes:Numbers above bars denote % of subjects reporting with any severity.
a. Fever: Oral temperature of >= 38.0°C., Grade 1: 38.0°C to 38.4°C; Grade 2: >38.5°C to 38.9°C; Grade 3: >39°C to 40.0°C; Grade 4: >40.0°C.
b. Vomiting: Grade 1: 1 to 2 times in 24 h; Grade 2: >2 times in 24 h; Grade 3: Requires intravenous hydration; Grade 4: Emergency room visit or hospitalization for hypotensive shock. c. Diarrhea: Grade 1: 2 to 3 loose stools in 24 h; Grade 2: 4 to 5 loose stools in 24 h; Grade 3: 6 or more loose stools in 24 h; Grade 4: Emergency room visit or hospitalization for severe diarrhea d. Headache/Fatigue/Tiredness/Chills/New or worsening muscle pain/new or worsening joint pain: Grade 1: Does not interfere with activity; Grade 2: Some interference with activity; Grade 3: Prevents daily routine activity; Grade 4: Emergency room visit or hospitalization for severe headache/fatigue/chills/severe new or worsened muscle pain/severe new or worsened joint pain
e. Nausea: Grade 1: No interference with activity or 1 to 2 episodes per 24 h; Grade 2: No interference with activity or >2 episodes per 24 h; Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Emergency room visit or hospitalization for hypotensive shock.
Data Extraction Date: 08AUG2022, Source: f14_2_7_2_1_1_sys_sev.sas, Date/time of run: 17AUG2022 11:39 Page 10 of 10

Systemic reactions cohort 4

Figure 12. Systematic Events, by Maximum Severity, Within 7 Days of Study Vaccination – Cohort 4 Participants 18 to 85 Years of Age (Part A and Part B: Booster Dose, Dose 3) – BNT162b2 (B.1.617.2) – Reactogenicity Set



Systemic Events, by Maximum Severity, Within 7 Days of Study Vaccination - Cohort 4 Participants 18 to 85 Years of Age (Part A and Part B: Booster Dose, Dose 3) - BNT162b2 (B.1.617.2) - Reactogenicity Set



Date of Cut Off: Cohort 4 Part A:12Oct2021 and Cohort 4 Part B:10Jan2022. Notes:Numbers above bars denote % of subjects reporting with any severity.
a. Fever: Oral temperature of >= 38.0°C., Grade 1: 38.0°C to 38.4°C; Grade 2: >38.5°C to 38.9°C; Grade 3: >39°C to 40.0°C; Grade 4: >40.0°C.
b. Vomiting: Grade 1: 1 to 2 times in 24 h; Grade 2: >2 times in 24 h; Grade 3: Requires intravenous hydration; Grade 4: Emergency room visit or hospitalization for hypotensive shock. c. Diarrhea: Grade 1: 2 to 3 loose stools in 24 h; Grade 2: 4 to 5 loose stools in 24 h; Grade 3: 6 or more loose stools in 24 h; Grade 4: Emergency room visit or hospitalization for severe diarrhea d. Headache/Fatigue/Tiredness/Chills/New or worsening muscle pain/new or worsening joint pain: Grade 1: Does not interfere with activity; Grade 2: Some interference with activity; Grade 3: Prevents daily routine activity; Grade 4: Emergency room visit or hospitalization for severe headache/fatigue/chills/severe new or worsened muscle pain/severe new or worsened joint pain
e. Nausea: Grade 1: No interference with activity or 1 to 2 episodes per 24 h; Grade 2: No interference with activity or >2 episodes per 24 h; Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Emergency room visit or hospitalization for hypotensive shock.
Data Extraction Date: 08AUG2022 Source: f14_2_7_2_1_4_sys_sev.sas, Date/time of run: 17AUG2022 11:39 Page 10 of 10

While cross-study comparisons, and particularly cross-study comparisons of AE reporting, is fraught with uncertainty, there appears to be a tendency that the rate of severe systemic reactions is somewhat higher with alpha/delta and delta compared to other variants tested.

Adverse events

Cohort 1: BNT162b2 (B.1.1.7 + B.1.617.2)

A total of 14.1% of participants reported any AE after study vaccination (booster dose, Dose 3) across both age groups (range: 7.9% to 19.0%). AEs were generally reported at a lower frequency in 56 to 85 years of age group. There were no SAEs, AESIs or deaths reported in this cohort.

Many AEs were consistent with reactogenicity events that were reported as AEs (e.g., injection site pain, fatigue, and diarrhoea), which showed no clinically meaningful imbalance between age groups. All AEs were mild or moderate in severity (Table 14.3.1.6_1).

There were no reported events of myocarditis or pericarditis (protocol-defined AESIs).

Lymphadenopathy or terms consistent with lymphadenopathy (lymphadenitis) were reported in 1.1% of participants. A participant in the 45 to 54 year age group reported a nonserious event of drug hypersensitivity (allergic reaction to drug) with onset Day 2 of Dose 1, moderate in severity that was considered related to the study intervention by the investigator. The event was reported as resolved at the time of data cutoff date.

Cohort 4: BNT162b2 (B.1.617.2)

A total of 12.1% of participants reported any AE after study vaccination (booster dose, Dose 3) across both age groups (range: 9.9% to 15.0%). AEs were generally reported at a lower frequency in the 56 to 85 years of age group. Related AEs were reported by 17 (4.6%) participants. There were no SAEs or deaths reported in this cohort.

Many AEs were consistent with reactogenicity events that were reported as AEs (eg, injection site pain, fatigue, and headache), which showed no clinically meaningful imbalance age groups. Most AEs were mild or moderate in severity.

Lymphadenopathy was reported in 1.3% of participants.

One (0.3%) participant reported an AESI of myocarditis: A participant in the 25 to 34 year age group who had a history of a stress-induced "fluttering heart" with a normal ECG in 2020, was reported to have a nonserious event of myocarditis (verbatim per investigator was "probable myocarditis"). Approximately 36 hours (in November 2021) after being vaccinated with a booster dose of BNT162b2 (B.1.617.2) 30 µg the participant experienced 'persistent chest pain' which lasted about 3 hours and tachycardia for approximately 13 hours for which the participant took ibuprofen 200 mg every 4 to 6 hours from pain onset to the following day. The participant visited the site 3 days later, being asymptomatic and was revealed to have an elevated Troponin I (350 ng/L; upper range: 47 ng/L) and nonspecific ECG abnormalities (Sinus rhythm, abnormal q and Q Wave [III, V6], low voltage [chest leads]); an echocardiogram was normal. The event of myocarditis was considered to be recovered within 9 days based on normalization of troponin I level and no ECG abnormalities. The participant was never hospitalized. The myocarditis was assessed by the investigator and sponsor as related to vaccination.

5.2.3 Study C4591044 - bivalent (Original + Omicron BA.4/BA.5)

Study C4591044 is evaluating BNT162b2 bivalent (Original + Omicron BA.4/BA.5) vaccine in the United States in individuals 12 years of age and older through amendments 1 and 2. The projected dates provided below refer to availability of tables, listings and figures: relevant submissions will be planned accordingly as soon as possible following availability of TLFs and depending on the required submission format.

Amendment 1 will generate descriptive safety and immunogenicity data in 500 individuals receiving the 30 µg bivalent (Original and Omicron BA.4/BA.5) vaccine (at least 100 in each age group: 12-17 years, 18-55 years, >55 years) which are anticipated to be available as follows:

1. 7 day reactogenicity data – 29th September 2022
2. 1 month safety (all participants) and sentinel immunogenicity (30 participants in each age group 18-55 and >55 years) using non-validated BA.4/BA.5 neutralization assay – end October 2022
3. 1 month immunogenicity (all participants) using validated BA.4/BA.5 neutralization assay – December 2022

Amendment 2 will be initiated in the second half of September and will generate additional safety and immunogenicity data in a further 400 individuals receiving the 30 µg bivalent (Original and Omicron BA.4/BA.5) vaccine (200 in each age group: 18-55 years, >55 years) for hypothesis-driven immunogenicity analyses which are anticipated to be available as follows:

4. 1 month safety and immunogenicity (all participants) using validated BA.4/BA.5 neutralization assay – January 2023

All participants will be followed for serious adverse events and immunogenicity through 6 months after vaccination, which will be reported in the final clinical study report.

5.2.4 Discussion on clinical safety

Inferences on the reactogenicity and safety of Original/BA.1 are based on extrapolation from the very large safety database for Comirnaty Original, as well as the broadly similar overall acceptable reactogenicity shown for boosting with Original and for variant vaccines including monovalent beta, delta and BA.1, as well as bivalent alpha/delta and Original/BA.1.

While two randomised studies have indicated marginally greater systemic reactogenicity when BA.1 is a component of the vaccine, compared to Original alone, this difference is not clinically meaningful.

Moreover, the frequency of severe systemic reactogenicity events is numerically higher when administering delta or alpha/delta variant vaccines, although a caveat about cross study comparisons is relevant:

Table 6. Participants Reporting Local Reactions and Systematic Events Within 7 Days Post Dose 3 or Dose 4 of BNT162b2, Monovalent BNT162b2 OMI, Bivalent BNT162b2+BNT162b2 OMI or BNT162Bt$_{SA}$ at 30 µg Dose Level in Studies C4591001, Studies C4591031 Substudy D and C4591031 Substudy E

Events	C4591031 Substudy D[a] (18 to 55 Years)		C4591031 Substudy E[b] (>55 Years)			C4591001[c] (18 to 55 Years)	
	BNT162b2 OMI 30 µg	BNT162b2 30 µg	BNT162b2 30 µg	BNT162b2 OMI 30 µg	BNT162b2 + BNT162b2 OMI 30 µg	BNT162b2 30 µg	BNT162b2$_{SA}$ 30 µg
	Dose 4 (N=294)	Dose 4 (N=306)	Dose 4 (N=298)	Dose 4 (N=301)	Dose 4 (N=301)	Dose 3 (N=289)	Dose 3 (N=298)
Local reaction at injection site: Total (Severe)*							
Pain	77.9% (0.7%)	78.4% (1.0%)	60.1% (0.3%)	66.1% (0%)	58.1% (0.3%)	83.0% (0.3%)	82.9% (1.0%)
Swelling	8.5% (0%)	8.8% (0%)	6.0% (0%)	8.3% (0%)	6.6% (0%)	8.0% (0.3%)	6.7% (0.3%)
Redness	7.1% (0%)	4.2% (0%)	6.4% (0.3%)	6.3% (0.3%)	7.0% (0%)	5.9% (0%)	5.0% (0.3%)
Systemic events: Total (Severe)*							
Fatigue	64.3% (3.4%)	60.5% (2.6%)	45.3% (0.3%)	52.5% (2.7%)	49.2% (1.7%)	63.7% (4.5%)	69.8% (4.7%)
Headache	47.6% (2.0%)	45.1% (2.0%)	26.5% (0.3%)	36.5% (1.0%)	33.6% (0.3%)	48.4% (1.0%)	53.0% (1.3%)
Muscle pain	33.7% (0.7%)	28.4% (1.0%)	19.8% (0%)	23.9% (0.3%)	22.3% (0%)	39.1% (1.4%)	38.6% (2.0%)
Chills	31.6% (1.4%)	26.1%(1.0%)	16.4% (0%)	25.6% (0.7%)	13.0% (0%)	29.1% (1.0%)	36.6% (2.0%)
Joint pain	23.5% (1.0%)	15.0% (0%)	9.1% (0%)	16.6% (0%)	11.3% (0%)	25.3% (0.3%)	22.5% (0.7%)
Fever (≥38.0°C)	8.5% (0.3%)	7.2% (0.3%)	3.7% (0%)	8.3% (1.0%)	5.0% (1.3%)	8.7% (0.3%)	9.4% (1.3%)
Vomiting	2.7% (0%)	1.6% (0%)	1.3% (0%)	3.0% (0%)	1.7% (0%)	1.7% (0%)	0.7% (0%)
Diarrhea	8.5% (0%)	11.8% (0.7%)	4.4% (0%)	8.0% (0.7%)	9.0% (1.3%)	8.7% (0%)	9.7% (0.3%)
Use of Antipyretic or pain medication[d]	38.8%	39.5%	26.8%	34.9%	29.2%	46.7%	45.3%

a. BNT162b2-experienced participants (18 to 55 years of age) who received either BNT162b2 30 µg or BNT162b2 OMI 30 µg as a booster (Dose 4) approximately 3 to 6 months (90 to 180 days) after their last dose (Dose 3).
b. BNT162b2-experienced participants (>55 years of age) who received BNT162b2 30 µg or BNT162b2 OMI 30 µg or BNT162b2 + BNT162b2 OMI 30 µg as a booster dose (Dose 4) approximately 5 to 12 months after their last dose (Dose 3).
c. BNT162b2-experienced participants (18 to 55 years of age) who were randomized to receive a booster (Dose 3) dose of BNT162b2 30 µg or BNT162b2SA 30 µg approximately 6 months after their second dose of BNT162b2 30 µg (Dose 2).
d. Severity was not collected for use of antipyretic or pain medication.
* No Grade 4 events were reported.

	BNT 162-17 Part B cohort 1		BNT 162-17 Part B cohort 4	
	Alpha+Delta Dose 3		Delta Dose 3	
Age group	18-55	56-85	18-55	56-85
	N=220	N=121	N=206	N=140
	Any reported reacogenicity events %(severe events%)			
Local reaction at injection site				
Pain at injection site	78.2% (7.3%)	67.8%(0.8%)	81.1% (4.9%)	67.9% (0.7%)
Swelling	8.2% (1.4%)	14.9%(1.7%)	9.2% (0%)	7.9 %(1.4 %)
Redness	7.7%(2.3%)	14% (3.3%)	9.7% (1%)	7.1%(0%)
Systemic events				
Fatigue	69.1% (8.6%)	55.4% (5.8%)	68.9%(10.7%)	55%(5.0%)
Fever(≥38.0°C)	10.5% (1.4%)	7.4%(0%)	10.7% (1.5%)	8.6% (2.1%)
Headache	51.4% (3.6%)	38.8% (2.5%)	58.7% (4.4%)	40.7% (2.9%)
Muscle pain	36.8% (5.5%)	34.7% (1.7%)	42.2% (4.4%)	31.4%(2.1%)
Chills	27.7% (4.5%)	24.8% (1.7%)	36.9% (5.8%)	27.9%(5.0%)
Joint pain	27.7% (2.7%)	20.7% (0.8%)	25.7% (2.4%)	17.9% (1.4%)
Vomiting	1.8% (0%)	2.5% (0%)	1.5%(0%)	2.9% (0%)
Diarrhea	4.5% (0.5%)	7.4% (0%)	13.6% (1%)	7.9% (0%)
% taking antipyretic meds	Data not yet analyzed			

In summary, the CHMP is of the view that it is deemed unlikely that the reactogenicity of BA5/Original would not be clinically acceptable. Reactogenicity data from 500 subjects 18 years and older, are anticipated to be delivered by the company on the 29th September.

It is noted by the CHMP that there were two incident cases of diabetes mellitus in the study of primary vaccination with the beta variant: one case of treatment emergent diabetes mellitus type 1 in a participant in the 25 to 34 year age group, diagnosed approximately 6 weeks after the first vaccination with the beta variant vaccine. Another case was a case of diabetes mellitus, type not described, in an obese participant in the 45 to 54 year age group with a family history of type 2 diabetes. The diagnosis is about four months after the first beta vaccination, and the subject is described as asymptomatic. While type 1 diabetes cannot be excluded, this seems improbable.

Thus, it is not likely that there was more than one incident case of type 1 diabetes in the study. The CHMP is of the opinion that this does not raise a specific concern in the context of the importance of spike protein sequence for less common side effects. Diabetes Mellitus type 1 is not listed as an AE of Comirnaty, as there has been no indication so far that this is causally related to vaccination. It is suggested that this be followed in the PSUR cycle.

5.2.5 Conclusions on clinical safety

In the cumulative experience of Comirnaty Original and variant vaccines with differing spike protein sequences, the CHMP is of the view that the reactogenicity has been acceptable at a total dose of 30ug. It is considered unlikely that the Original/BA.4-5 would differ in this respect.

The CHMP also noted that data on reactogenicity from ongoing study C4591044 are anticipated in September/October 2022.

6. Risk management plan

The MAH submitted an updated RMP **version 7.1** (date of final sign off September 2022) with this application.

The (main) proposed RMP changes were the following (reflected in purple font):

RMP Part/Module	RMP v 7.1 Major Changes
PRODUCT(S) OVERVIEW	Addition of Comirnaty Original/Omicron BA.4-5 (15/15 mcg) data according to the updated SmPC.
SAFETY SPECIFICATION	
Epidemiology of the Indication(s) and Target Populations	Updated with new DLP and new data for Omicron variants.
Non-Clinical Part of the Safety Specification	Minor update with animal immunogenicity data for BA.4-5
Clinical Trial Exposure	No changes made.
Populations Not Studied in Clinical Trials	No changes made.
Post-Authorisation Experience	Updated with new DLP 18 June 2022.
Additional EU Requirements for the Safety Specification	No changes made.
Identified and Potential Risks	Minor update on B/R of pregnancy/breast feeding and immunocompromised patients according to the updated SmPC for BA.4-5
Summary of the Safety Concerns	No changes made.
PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	
Routine Pharmacovigilance activities	Updated to add Comirnaty Original/Omicron BA.4/5 (15/15 mcg) formulation in the vial differentiation description.
Additional Pharmacovigilance Activities and Summary Table of Additional Pharmacovigilance Activities	Inclusion of 2 new interventional studies as additional PV activity: C4591031 and C4591044. Addition of updated text for C4591014 and WI255886 that will also assess the effectiveness of the bivalent Omicron modified vaccines following their introduction. Updates of other non-interventional studies (C4591012, C4591021 and C4591036) to be assessed for the feasibility of studying the bivalent Omicron modified vaccine
PLANS FOR POST AUTHORISATION EFFICACY STUDIES	No changes made.
RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	

Routine Risk Minimisation Measures Additional Risk Minimisation Measures Summary of Risk Minimisation Measures	Updated based on the changes made in PART III.
SUMMARY OF THE RISK MANAGEMENT PLAN	
I The Medicine and What It Is Used For II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks	Updated to include Comirnaty Original/Omicron BA.4-5 (15/15 mcg) Updated based on the changes made in PART III and PART V.
ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 2: Studies/milestones updated Annex 3: Addition of the 2 new studies C4591031 and C4591044 Annex 8: Changes to reflect the updates

Note that **relevant parts** only (e.g. summary of the safety concerns, pharmacovigilance plan etc.) including **relevant parts from the RMP covering proposed changes** are reproduced in the sections below. All administrative and editorial changes in other parts of the RMP are accepted.

Summary of safety concerns

No changes were made to the Summary of safety concerns

Table SVIII.1: 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

The MAH proposed no changes to the summary of safety concerns.

PRAC considers the safety concerns listed above remain appropriate.

Pharmacovigilance plan

ROUTINE PHARMACOVIGILANCE ACTIVITIES

[…]

Vial differentiation

All vials have specific color flip off plastic cap and label differentiation factors:

Table 7. Vaccine Presentation Characteristics

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

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

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 (i.e.. less than 12 years and above 12 years of age). This represents the likelihood of the purple and grey 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 resources and referenced materials for healthcare providers.

Note that various information resources (e.g. poster, dosing card, medical information call centres, traceability and vaccination reminder card) were 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.

Although all vials have specific colour flip off plastic cap and label differentiation factors, expert input from clinical practice raised concerns about the same colour flip off for 'Comirnaty original' and the new bivalent vaccine. With launch of the modified vaccines the MAH was requested to commit to again carefully monitor Medication errors and inform the Rapporteur immediately in case of any unexpected findings or trends (RfSI II-140). The MAH responded that they agree and confirm the commitment to continue monitoring medication errors as part of their routine pharmacovigilance activities. Any unexpected findings or trends will be duly notified to the EMA, which is accepted.

ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The MAH proposes the following 19 studies, of which 5 global, 5 in Europe only, 6 in US only, 2 in US and Canada and 1 in New Zealand. There are 8 interventional studies (C4591001, C4591007, C4591015, BNT162-01 Cohort 13, C4591024, **C4591031, C4591044** and 1 study for vaccine interactions), 3 Low-Interventional studies (C4591036, WI235284 and WI255886) and 8 non-interventional studies (7 safety and 1 effectiveness), summarised in the table below and further detailed in the summary table of ongoing and planned additional pharmacovigilance activities.

Study Number	Country	Interventional/ non-Interventional/ Low-Interventional	Purpose
C4591001	Global	Interventional	Safety
C4591007	Global	Interventional	Safety
C4591015	Global	Interventional	Safety
C4591024[a] (former Safety and immunogenicity in high-risk adults)	Global	Interventional	Safety
C4591030 (Co-administration study with seasonal influenza vaccine)	NZ	Interventional	Safety
C4591031	**Global**	**Interventional**	**Safety Effectiveness**
C4591044	**US**	**Interventional**	**Safety Effectiveness**
BNT162-01 Cohort 13	EU	Interventional	Safety
C4591009	US	non-Interventional	Safety
C4591010	EU	non-Interventional	Safety
C4591011	US	non-Interventional	Safety
C4591012	US	non-Interventional	Safety
C4591021 (former ACCESS/VAC4EU)	EU	non-Interventional	Safety
C4591022	US/CA	non-Interventional	Safety
C4591038 (former C4591021 substudy)	EU	non-Interventional	Safety
C4591014	US	non-Interventional	Effectiveness[b]
WI235284	US	Low-Interventional[c]	Effectiveness
WI255886	EU[d]	Low-Interventional	Effectiveness
C4591036 (former Pediatric Heart Network)	US/CA	Low-Interventional	Safety

a. Based on the outcome of procedures PAM-MEA-015.2 and PAM-MEA-016, and in particular based on the conclusions of the Assessment Report for the Post-Authorisation Measure MEA/015.2 and MEA/016 (EMA/CHMP/498689/2021) issued on 16 September 2021, the design of study C4591024 was agreed to satisfactorily cover the objectives initially planned for study C4591018, that is therefore removed from the list of studies

b. Vaccine effectiveness is not a safety concern.

c. The study does not involve any administration of vaccine or other Pfizer products but since a specimen collection procedure is required per protocol, this qualifies this study as 'low-interventional'.

d. United Kingdom.

Non-Interventional Post-Approval Safety Studies Assessing Myocarditis/Pericarditis

[…]

In addition, studies C4591012, C4591021, and C4591036 will be assessed for the feasibility of studying the bivalent Omicron-modified vaccine. 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.

With the assessment of the BA.1 bivalent vaccine (II/0140), the CHMP AR stated that 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 BA.1 bivalent vaccine as well as future modified vaccines (of which the BA.4/.5 bivalent vaccine is one) in all ongoing PASSs or otherwise justify. In addition, the MAH was requested to commit to submit the PASS protocol amendments as soon as possible after finalizing this variation application.

The *MAH responded* during variation II/0140 that they will assess the feasibility of studying the bivalent vaccine and future modified vaccines in studies C4591012, C4591021, and C4591036, which is not accepted In addition, the *MAH noted* that feasibility is dependent on the ability to uniquely identify the bivalent vaccine and future modified vaccines as the booster dose administered. However, PRAC considers that due to measures implemented by the MAH (e.g. differences in naming, labelling), the bivalent vaccine will be uniquely identified.

Moreover, concerning the ongoing safety studies with the initial monovalent vaccine (including booster doses) so far one or two interim reports were submitted for assessment by the EMA and subsequently limited (follow-up) safety data from the PASSs is available yet. Therefore, these safety studies should include the BA.1 bivalent vaccine as well as the BA.4/.5 bivalent vaccine in all (ongoing) PASSs or otherwise justify with methodological issues or other issues (within 3 months after approval of the bivalent vaccine).

The MAH noted that where feasible, amended protocols for studies C4591012, C4591021, and C4591036 will be submitted within 3 months after authorization of the bivalent vaccine, which is accepted.

The MAH's agreement to include the BA.1 bivalent vaccine as well as the BA.4/.5 bivalent vaccine in all currently ongoing PASS (studies C4591009, C4591010, C4591012, C4591021, C4591022) and study C4591036 is considered acceptable. For studies with an interim/monitoring report to be submitted within the next 6 months, protocol amendments can be submitted with the next interim report. Otherwise, a stand-alone protocol update should be submitted within 3 months.

For studies for which no protocol amendment is proposed by the MAH e.g. due to any methodological or other issues, a justification will be submitted within 1 month after finalisation of the current variation.

Study (*study short name, and title*) **Status *(planned/on-going)***	**Country**	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
Category 2					
C4591001 *Ongoing*	Global	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine. An imbalance between the vaccine and control groups in the frequency of	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in frail patients with co-morbidities (C4591001 subset)	CSR submission upon regulatory request:	Any time
				CSR submission 6 months post Dose 2:	31-May-2021

Study (*study short name, and title)* **Status** ***(planned/on-going)***	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
		COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.	Long term safety data.	Final CSR submission with supplemental follow-up:	31-Dec-2023
C4591007 *Ongoing*	Global	The purpose of the dose-finding/selected-dose study is to rapidly describe the safety, tolerability, immunogenicity, and efficacy of the BNT162b2 RNA-based COVID-19 vaccine candidate against COVID-19 in healthy children.	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long term safety data.	Final CSR submission:	03-Dec-2024

Study (*study short name, and title)* **Status** ***(planned/on-going)***	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
Category 3					
C4591009 *Ongoing*	US	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, among individuals in the general US population and in subcohorts of interest within selected data sources participating in the US Sentinel System.	Myocarditis and pericarditis AESI-based safety events of interest Use in pregnancy Use in immunocompromised patients	Protocol submission:	31-Aug-2021
				Protocol amendment submission:	11-Jul-2022
				Monitoring report 1 submission:	31-Oct-2022
				Monitoring report 2 submission:	31-Oct-2024
				Interim Analysis submission:	31-Oct-2023
				Final CSR submission:	31-Mar-2026
C4591011 *Planned*	US	To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine.	Myocarditis and pericarditis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission:	30-Sep-2022
					31-Dec-2022
				Final CSR submission:	31-Dec-2023
C4591012 *Ongoing*	US	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine	Myocarditis and pericarditis AESI-based safety events of interest including vaccine associated enhanced disease	Interim reports submission:	30-Jun-2021
					31-Dec-2021
					30-Jun-2022
					31-Dec-2022

Study (*study short name, and title)* **Status** *(planned/on-going)*	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
		including the bivalent Omicron modified vaccine, if feasible.	Use in immunocompromised patients. Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Final CSR submission	31-Dec-2023
C4591010 *Ongoing*	EU	To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates.	AESI-based safety events of interest Use in pregnancy Long-term safety data.	Final CSR submission	30-Sep-2024
C4591015 *Ongoing*	Global	To assess safety and immunogenicity in pregnant women In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.	Use in pregnancy and while breast feeding.	Final CSR submission:	30-Apr-2023
C4591014 *Ongoing*	US	To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation and emergency department	Not Applicable.	Final CSR submission:	30-Jun-2023

Study (*study short name, and title)* **Status** ***(planned/on-going)***	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
		admission for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction.		Protocol amendment (for bivalent Omicron-modified vaccine) submission:	31-Dec-2022
				Final CSR (for bivalent Omicron-modified vaccine) submission:	30-Jun-2024
WI235284 *Ongoing*	US[a]	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Final CSR submission:	30-Jun-2023
WI255886 *Ongoing*	Ex-EU[a,b]	To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction.	Not Applicable.	Final CSR submission:	30-Jun-2023
				Protocol amendment (for bivalent Omicron-modified vaccine) submission:	31-Dec-2022
				Final CSR (for bivalent Omicron-modified vaccine) submission:	30-Jun-2024
BNT162-01 Cohort 13 *Ongoing*	EU	To assess potentially protective immune responses in immunocompromised adults.	Use in immunocompromised patients.	IA submission:	30-Sep-2021
				Final CSR submission:	31-Oct-2023**Error! Bookmark not defined.**
C4591024 (former Safety	Global	Safety, tolerability and immunogenicity based on		Protocol submission:	30-Jun-2021

Study (*study short name, and title)* **Status *(planned/on-going)***	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
and immunogenicity in high-risk adults) *Ongoing*		representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal disease).	Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders.	Final CSR submission:	30-Jun-2023
C4591021 (former ACCESS/VAC4EU) *Ongoing*	EU	Assessment of potential increased risk of adverse events of special interest (AESI) after being vaccinated with COVID-19 mRNA vaccine including bivalent Omicron modified vaccine, if feasible. Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.	Myocarditis and Pericarditis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long term safety data.	Final CSR submission:	30-Sep-2024
C4591038 (former C4591021 substudy) *Planned*	EU	To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine.	Myocarditis and Pericarditis Long term safety data.	Protocol submission: Final CSR submission:	31-Jan-2022 30-Sep-2024
C4591022 *Ongoing*	US/CA	To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations,	Use in pregnancy.	Interim reports submission:	31-Jan-2022 31-Jan-2023 31-Jan-2024

Study (*study short name, and title*) **Status** *(planned/on-going)*	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
		spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age.		Final CSR submission:	31-Dec-2024
C4591036 (former Pediatric Heart Network Study) *Planned*	US/CA	To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis including myocarditis after the bivalent Omicron modified vaccine, if feasible	Myocarditis/pericarditis Long term safety data.	Protocol submission:	30-Nov-2021
				Final CSR submission:	31-Dec-2029
C4591030 (Co-administration study with seasonal influenza vaccine) *Ongoing*	Not available	Safety and immunogenicity of COVID-19 mRNA vaccine and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines.	Protocol submission:	17 Aug 2021
				Final CSR submission:	31-Dec-2022
C4591031 Substudy E *Ongoing*	Global	To describe the safety and tolerability profile of BNT162b2 (30 and 60 µg), BNT162b2 OMI (30 and 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants >55 years of age. To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in participants 18 to 55 years of age.	Not applicable[c] Reactogenicity as partial proxy to the general safety profile	Interim reports submission (> 55 y):	31-Aug-2022
				Interim reports submission (18 - to 55 y):	31-Oct-2022
				6M Final CSR submission (>55 y):	31-Jan-2023
				6M Final CSR submission (18- to 55 y):	30-Mar 2023
C4591044 *Ongoing*	US	To describe the safety/tolerability and immune response to BNT162b5 Bivalent and BNT162b2 Bivalents given as a 2nd booster dose to COVID-19-vaccine-experienced participants ≥12 years of age.	Not applicable[c] Reactogenicity as partial proxy to the general safety profile	Protocol Submission:	14-Jun-2022
				Protocol amendment 1 submission:	28-Jul-2022
				Final CSR submission:	30-Sep-2023

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

Ongoing, interventional safety and effectiveness studies C4591031 and C4591044 were added as additional pharmacovigilance studies in the RMP, see above Summary table.

C4591031

The objectives of study C4591031 are:

1. To describe the safety and tolerability profile of BNT162b2 (30 and 60 µg), BNT162b2 OMI (30 and 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants >55 years of age.
2. To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in participants 18 to 55 years of age.

For further details on this study including sub-studies, please refer to the Clinical AR (II-140). In variation application II-140 a further follow up of immunogenicity and safety data with the bivalent vaccine Original/Omicron BA.1 in individuals 18 to 55 years old in the ongoing study C4591031 was requested as a commitment. The MAH agrees and noted that for the sake of clarity, study C4591031 substudy E has already been proposed and agreed by PRAC for inclusion as an Additional Pharmacovigilance measure (Category 3 study), including relevant milestones, in RMP v7.0 submitted on 15 August 2022 in the context of Variation II/0143.

C4591044

For study C4591044, the MAH provided the following information in writing, apart from the RMP submission:

Study C4591044 is evaluating BNT162b2 bivalent (Original + Omicron BA.4/BA.5) vaccine in the US in individuals 12 years of age and older through amendments 1 and 2. The projected dates provided below refer to availability of tables, listings and figures: relevant submissions will be planned accordingly as soon as possible following availability of TLFs and depending on the required submission format.

Amendment 1 was initiated last week and will generate descriptive safety and immunogenicity data in 500 individuals receiving the 30 µg bivalent (Original and Omicron BA.4/BA.5) vaccine (at least 100 in each age group: 12-17 years, 18-55 years, >55 years) which are anticipated to be available as follows:

1. *7 day reactogenicity data – end September 2022*
2. *1 month safety (all participants) and sentinel immunogenicity (30 participants in each age group 18-55 and >55 years) using non-validated BA.4/BA.5 neutralization assay – end October 2022*
3. *1 month immunogenicity (all participants) using validated BA.4/BA.5 neutralization assay – December 2022*

Amendment 2 will be initiated in the second half of September and will generate additional safety and immunogenicity data in a further 400 individuals receiving the 30 µg bivalent (Original and Omicron BA.4/BA.5) vaccine (200 in each age group: 18-55 years, >55 years) for hypothesis-driven immunogenicity analyses which are anticipated to be available as follows:

1. *1 month safety and immunogenicity (all participants) using validated BA.4/BA.5 neutralization assay – January 2023*

All participants will be followed for serious adverse events and immunogenicity through 6 months after vaccination, which will be reported in the final clinical study report.

Regarding the pharmacovigilance plan, PRAC endorsed the inclusion of studies C4591031 and C4591044 since these studies will provide reactogenicity and immunogenicity data shortly. However, PRAC noted that due to their sample size, the newly included studies will not be able to characterise the important identified risks of myocarditis/pericarditis and important potential risks of VAED/VAERD.

For studies C4591031 and C4591044, 'Myocarditis and Pericarditis, Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)' was removed from the column Safety concerns addressed and replaced with "reactogenicity as partial proxy to the general safety profile".

Risk minimisation measures

This section has been updated based on the changes made in PART III.

Routine risk minimization measures

The product information is sufficient to mitigate the current identified and potential risks of COVID-19 mRNA vaccine. The necessary information to ensure appropriate use of the product is included in the relevant sections of the SmPC. No additional measures for risk minimisation are considered necessary by the MAH at this time.

Additional risk minimization measures

None.

As the summary of safety concerns remains unchanged and no new safety concerns have been identified, routine risk minimization measures remain sufficient to mitigate the important risks.

The risk of medication errors associated with the introduction of bivalent vaccines has thoroughly been discussed in variation II/0140 (bivalent BA.1 vaccine) and it was concluded that routine risk minimization measures are sufficient. The same applies with the bivalent vaccine currently under evaluation.

In conclusion, the RMP version 7.1 is considered acceptable.

7. Change to the product information

As a consequence of this new indication, relevant affected sections of the SmPC, Labelling text and PL for all presentations have been updated. Please see annotated attachment.

Labelling exemptions

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

Labelling exemptions

Outer labelling (from start of supply to end December 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

- Strength: '15/15 micrograms per dose' (initially proposed)', instead of '(15/15 micrograms)/dose' (agreed during evaluation with brackets).
- Statement of the active substance: "One dose contains 15 micrograms tozinameran and 15 micrograms mRNA encoding Omicron BA.4 and BA.5", instead of "One dose contains 15 micrograms tozinameran and 15 micrograms famtozinameran" (agreed during the assessment)".
- 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/ famtozinameran' (during evaluation).
- "(Each vial contains 6 doses of 0.3 mL.)" with text brackets (initially proposed) instead of " "Each vial contains 6 doses of 0.3 mL" without brackets (agreed during evaluation).
- MA number with 'XXX' placeholder, instead of MA number will be used after approval.

Box label

- Strength: '15/15 micrograms per dose' (initially proposed)', instead of '(15/15 micrograms)/dose' (agreed during evaluation with brackets).
- Statement of the active substance: "One dose contains 15 micrograms tozinameran and 15 micrograms mRNA encoding Omicron BA.4 and BA.5", instead of "One dose contains 15 micrograms tozinameran and 15 micrograms famtozinameran" (agreed during the assessment)".
- 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/ famtozinameran'' (during evaluation).
- "(Each vial contains 6 doses of 0.3 mL.)" with text brackets (initially proposed) instead of " "Each vial contains 6 doses of 0.3 mL" without brackets (agreed during evaluation).
- MA number with 'XXX' placeholder, instead of MA number will be used after approval

Quick Response (QR) code

- The updates of the QR code/URL to include further references to Comirnaty Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5, as well as the necessary layout changes on the website shall be submitted and assessed via an Article 61.3 notification (post-authorisation).

8. Overall conclusion and impact on the benefit-Risk Balance

Disease or condition

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

The sought indication is for booster use:

"Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19 (see sections 4.2 and 5.1)."

Available therapies and unmet medical need

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

Bivalent variant mRNA vaccines containing the original strain as well as BA.1. were approved for boosting in the EU beginning of September (similar indication as the one presently sought). However, Sars-Cov-2 evolution has been rapid, and as stated above the dominating variant at the present time is no longer BA.1 but BA.5.

Established principles of immunology as well as some preclinical immunogenicity data, indicate that a vaccine targeting BA.5 would optimise immunogenicity against BA.5, which might be translated into greater vaccine efficacy. Given the dynamic nature of the pandemic, and that it cannot be predicted what strain will cause the next wave, there is a benefit of having different vaccines available that can be used as booster.

It has been proposed that an adapted bivalent vaccine with the BA.4-5 spike protein sequence substituting for half of the content of the Original vaccine, might be approved based on widely accepted immunological principles, as well as the extrapolation of reactogenicity from the experience of different other variant vaccines.

Main clinical studies

There are no clinical data to support the approval of Original/BA4-5.

Favourable effects

It has been demonstrated that boosting with a bivalent Original/BA.1 vaccine confers increased immunogenicity against BA.1 compared to Original alone, as well as non-inferior immunogenicity to the original strain, while having the same total mRNA content. The CHMP is of the opinion that the

same would be the case for the Original/BA.4-5 vaccine versus BA.5 and the original virus. Data from immunogenicity studies in mice give some support for this notion.

Uncertainties and limitations about favourable effects

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

The former will be illustrated by immunogenicity data from study C4591044. Sentinel immunogenicity (30 participants in each age group 18-55 and >55 years) using non-validated BA.4/BA.5 neutralization assay are anticipated by mid November 2022. Immunogenicity for all participants using validated BA.4/BA.5 neutralization assay are foreseen for submission in December 2022.

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

Unfavourable effects

There is a very large safety database for Comirnaty Original, showing an acceptable safety profile.

Apart from Comirnaty Original, there are data on reactogenicity for Beta, Delta and Omicron BA.1 monovalent vaccine constructs. Moreover, there are reactogenicity data for bivalent Original/BA.1 and Alpha/Delta constructs. All of these demonstrate acceptable reactogenicity profiles.

Two randomised studies have indicated somewhat greater systemic reactogenicity when BA.1 is a component of the vaccine, compared to Original alone. However, this difference is not deemed clinically meaningful.

Uncertainties and limitations about unfavourable effects

The frequency of severe systemic reactogenicity events is numerically higher when boosting with delta or alpha/delta variant vaccines, though an important caveat relates to cross-study comparisons of reported safety.

It is not fully clarified to what extent and how the spike protein sequence matters for the degree of reactogenicity.

The assumption of acceptable reactogenicity and safety data are based on extrapolation from Comirnaty Original, as well as other monovalent and bivalent variant vaccines. While there may be minor differences in reactogenicity, there are presently no available data with the Original/BA.4-5 vaccine. Reactogenicity data from approximately 500 subjects 18 years and older, are anticipated to be delivered by the company within a few weeks of approval.

At the time when the abovementioned reactogenicity dataset has been submitted, the size of the safety database for BA.4-5 containing variant vaccines will still not be large enough to characterise the frequency of rare adverse events. However, it is notable that the only difference between Original/BA.4-5 and Original is in the spike protein sequence of BA.4-5.

There are no data on the bivalent Original/BA.4-5 variant vaccine in pregnancy. However, the total mRNA dose is the same as for Original, and no clinically meaningful difference in reactogenicity is expected based on the sum experience of Sars-Cov-2 variant vaccines. Moreover, the only difference

between products lies in the spike protein sequence. Therefore, based on the experience of Comirnaty Original, use in pregnancy is deemed acceptable.

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

While protection against severe disease remains high, the efficacy against any clinical disease of Comirnaty Original is obviously lower against Omicron strains, compared to what was seen against Wuhan and the Alpha-Delta variants.

It has been demonstrated that boosting with a bivalent BA.1/Wuhan vaccine with the same total amount of mRNA, yields higher immunogenicity versus BA.1, as well as non-inferior immune responses against Wuhan.

Based on established principles of immunology, the CHMP considers that a vaccine more closely matching what is presently circulating would optimise immunogenicity against that variant. It is also considered by the Committee that responses against the original Wuhan virus would not be inferior for a bivalent vaccine if the omicron component is BA.5 rather than BA.1.

The key uncertainty with respect to favourable effects is that the magnitude of any incremental clinical efficacy over and above available variants of Comirnaty is not known.

Regarding safety, there is a very large safety database for Comirnaty Original, showing an acceptable safety profile. The only difference between Original and Original/BA4-5 lies in the spike protein sequence, the total amount of mRNA being similar.

Apart from Comirnaty Original, there are data on reactogenicity when boosting with Beta, Delta and Omicron BA.1 monovalent vaccine constructs. Moreover, there are reactogenicity data for bivalent Original/BA.1 and Alpha/Delta constructs. All of these demonstrate acceptable reactogenicity profiles.

An thorough and swift approval is deemed helpful to cater to the public health needs related to ongoing vaccination campaigns, given the present epidemiological situation. Although the current BA.5 wave is declining in Europe, it cannot be predicted what variant will constitute the next wave. It is therefore considered by the CHMP beneficial to have different variant vaccines available that can be used in the vaccination campaigns.

While all variant COVID-19 vaccines up till now have had clinical data as basis of approval, the current approach is based on the paradigm for updating Influenza vaccines; here annual updates of the antigen sequence to match the currently circulating virus, are accepted without the need to provide clinical data; rather, efficacy and safety is inferred based on the cumulative experience of vaccine variants.

This is considered acceptable by the CHMP based on the established principles of immunology and the large amount of safety data available for Comirnaty vaccine variants.

In conclusion, the CHMP is of the opinion that an unacceptable reactogenicity profile when boosting with Original/BA.4-5 is considered sufficiently unlikely to allow for an early approval of the Original/BA.4-5, based on the Influenza paradigm. Interpretable reactogenicity data are anticipated within a month of approval, whereas immunogenicity data will be submitted somewhat later. The use of Original/BA.4-5 will be monitored by real life pharmacovigilance, as well as effectiveness studies.

Balance of benefits and risks

Given the evolution of Sars-Cov-2, the CHMP is of the view that the benefits of an early approval of Original/BA.4-5 outweighs the uncertainties related to extrapolations on immunogenicity and reactogenicity.

Conclusions

The overall B/R of Comirnaty Original/Omicron BA.4-5 is positive.

The following measures are considered necessary to address issues related to efficacy and safety:

- The delivery of immunogenicity and safety data from study C4591044 in accordance with the schedule that has been proposed by the applicant, i.e. for an expected submission date of December 2022.

- The MAH has committed submit the following safety data before the end of September 2022: The provision of reactogenicity data from approximately 500 subjects 18 years of age or older, receiving Original/Omicron BA.4-5 in the C4591044 study.

9. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		**Type**	**Annex(es) 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	II	I, IIIA, IIIB and A

Addition of a new strain (Omicron BA.4-5) resulting in a new Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection presentation. The SmPC, the Package Leaflet and Labelling are updated accordingly. A revised RMP version 7.1 has been approved.

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), tozinameran/famtozinameran (COMIRNATY Original/Omicron BA.4-5).

Table on conditions and recommendations

Area	Number	Description	Classification	Due date
Quality	1	The MAH should provide information on the theoretical protein sizes of the mature protein and variants thereof. In addition, the MAH should update the dossier with Figure 1. *BNT162 Omicron (BA.4/BA.5) Expressed Protein Size by In Vitro Translation*, as provided in response to the request for supplementary information.	REC	Q4/2022
Quality	2	The MAH should provide long term and accelerated stability data for the 1-month time point for active substance batch GH5745.	REC	Nov 2022
Quality	3	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.