EMADOC-1700519818-1717428
Committee for Medicinal Products for Human Use (CHMP)

Type II group of variations assessment report

Procedure No. EMA/VR/0000231586

Invented name: COMIRNATY

Common name: COVID-19 mRNA vaccine

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

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

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start date	19 November 2024	19 November 2024
☐	CHMP Rapporteur AR	16 December 2024	17 December 2024
☐	PRAC Rapporteur AR	20 December 2024	19 December 2024
☐	PRAC comments	3 January 2025	3 January 2025
☐	CHMP comments	6 January 2025	6 January 2025
☐	Updated PRAC Rapporteur AR	7 January 2025	n/a
☐	Updated CHMP Rapporteur AR	9 January 2025	9 January 2025
☐	Start of CHMP written procedure	14 January 2025	14 January 2025
☐	PRAC outcome	14 January 2025	14 January 2025
☒	CHMP Outcome	16 January 2025	16 January 2025

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CO	Clinical Overview
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
FDA	Food and Drug Administration
GMFR	geometric mean fold rise
GMT	geometric mean titre
HLA	human leukocyte antigen
IL-2	interleukin-2
IL-4	interleukin-4
IFNγ	interferon gamma
mRNA	messenger ribonucleic acid
n	number of participants
OMI	Omicron
PBMC	human peripheral blood mononuclear cell
RNA	ribonucleic acid
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TNFα	tumour necrosis factor alpha
US	United States
WT	wild-type

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 30 September 2024 an application for group of variations.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II
C.I.11.b	C.I.11.b Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required*	Variation type II

A grouped application consisting of:

C.I.11.b: Submission of an updated RMP version 13.1 in order to include Protocol amendment no. 5 where the study design and objectives were revised for an interventional study C4591048, a master phase 1/2/3 protocol to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b2 RNA- based vaccine candidate(s) in healthy children, listed as a category 3 study in the RMP.

C.I.13: Submission of the final report from study C4591044 listed as a category 3 study in the RMP. This is an interventional randomised, active controlled, Phase 2/3 Study to Investigate the Safety, Tolerability, and Immunogenicity of Bivalent BNT162b RNA-Based Vaccine Candidates as A Booster Dose In COVID-19 Vaccine–Experienced Healthy Individuals. The RMP version 13.1 has also been submitted.

The requested variation(s) proposed amendments to the amendments to the Risk Management Plan (RMP). There was no proposed changes for SmPC.

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

Within this variation, the MAH submitted the final clinical study report (CSR) for C4591044. This report includes the final data for study C4591044 (Cohort 2 and 3 combined). Study C4591044 is a randomised, active controlled, Phase 1/2/3 study investigating the safety, tolerability, and immunogenicity of BNT162b bivalent (Original/Omicron BA.4-5) at 30 or 60µg in participants in three age groups: 12-17 years, 18-55 years and >55 years. Bivalent (wild-type/omicron (WT/OMI) BA.4-5) was given as the fourth dose (second booster). The study was listed as a category 3 study in the RMP.

Immunogenicity data for 1-, 3- and 6-months post-booster in participants ≥12 years of age were presented. The 1 month post-booster data were evaluated earlier (EMEA/H/C/005735/II/0177/G). The aim of the currently presented immunogenicity analysis were to follow up the antibody persistance, to explore cross-neutralising antibodies to other new circulating omicron variants and describe the cell-mediated immunity after the vaccination with bivalent original/Omicron BA.4-5 vaccine. The analysis was descriptive, which was agreed to earlier. The methodology of this study has been assessed during earlier procedures and found to be acceptable.

Persistent antibody level were observed up to 6 months post-vaccination in all age groups regardless of baseline COVID-19 immune status. The adolescent group demonstrated higher neutralising antibody levels than adults and older adults as expected. All participants had high a level of neutralising antibodies

against wt strain at baseline due to recent vaccination (less than 1 year ago) with Original vaccine. Geometric mean titres (GMTs) were observed to be highest at 1 month after study vaccination and gradually decreased at 3 and 6 months after study vaccination. However, at the 6-month timepoint, GMTs were still considerably higher than the baseline value across all age groups.

The non-validated fluorescent focus reduction neutralization test (FFRNT) assay was used to evaluate cross-neutralising responses to Omicron XBB.1.5, XBB.1.16 and CH.1.1. The GMTs for these types were very low indicating limited cross-neutralisation for these types. No clinically important protection against COVID-19 caused by these types is expected after the bivalent Original/Omi BA.4-5 vaccination.

T-cell responses generally peaked at 1 week post-vaccination increased slightly post-Dose 1 and remained unchanged at all other timepoints. This trend was observed across both age groups and dose levels. There was a skewing of the CD4 T-cell population towards IFN-γ production rather than IL-4, suggesting a Th1-biased response. This is an expected result as Th1 cells are responsible for mediating a cellular immune response to virally infected cells, such as SARS-CoV-2.

The safety data provided in this study are the adverse events (AEs) and serious adverse events (SAEs) reported from study vaccination through 6 months vaccination in study C4591044. Methods and safety data for participants who received a 30 or 60-µg dose of BNT162b2 Original/BA.4-5 as Dose 4, including local reactions and systemic events recorded in the e-diary for 7 days after vaccination through 1-month after study vaccination were previously described in EMEA/H/C/005735/II/0177/G.

During the reporting interval, any AEs were reported in 10-14% of the participants. Among these events, 2-5% were considered related to study vaccination. The participants aged >55 years reported the lowest frequency of related AEs (2%). Most of the related AEs were consistent with reactogenicity and preferred terms (PTs) already included in the SmPC.

In total 13 participants reported SAEs. One participant in the age group 12 through 17 years of age reported alcohol poisoning, among the subjects aged 18-<55 years one participant reported diverticulitis and another hypotension. Nine participants aged >55 years reported SAEs which included arrhythmia, post-procedural infection, hypoglycaemia, hypokalaemia, Type 2 diabetes mellitus, adenocarcinoma pancreas, leukemia, prostate cancer, and urinary tract obstruction. One participant aged >55 years died due to left ventricular failure. None of the events were considered related to study vaccination.

No cases of myocarditis and/or pericarditis were reported up to 6 months after study vaccination.

No new safety concern was identified.

A total of 68 participants reported COVID-19 occurrence. Overall, the most frequently determined lineage was identified as XBB.1.5 (Omicron) which reflects the epidemiological situation of COVID-19 at that time.

No update of the product information has been proposed by the MAH, which is endorsed.

Study C4591048 is a Phase 1/2/3 master study to investigate the safety, tolerability, and immunogenicity of variant-adapted BNT162b2 RNA-based vaccine candidates. This report includes the changes in this study described in amendment 5 evaluated via this underlying Type II Variation Procedure. Protocol amendment 5 was predominantly targeted for Substudy E study design and was developed based on feedback from US FDA. The amendments are well reasoned and no loss of information is expected due to the removal of the Substudy E, Group 1 as this age and dose group is covered in Substudy A Phase 1. The amendments are therefore acceptable

The updates on the RMP are acceptable.

The benefit-risk balance of COMIRNATY remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		Type
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II
C.I.11.b	C.I.11.b Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required*	Variation type II

A grouped application consisting of:

C.I.13: Submission of the final report from study C4591044 listed as a category 3 study in the RMP. This is an interventional randomised, active controlled, Phase 2/3 Study to Investigate the Safety, Tolerability, and Immunogenicity of Bivalent BNT162b RNA-Based Vaccine Candidates as A Booster Dose In COVID-19 Vaccine–Experienced Healthy Individuals.

C.I.11.b: Submission of RMP version 13.2 in order to remove completed studies/milestones, update milestones from on-going studies, and introduce administrative and editorial changes. Protocol amendment no. 5 for study C4591048 was also submitted; this is a phase 1/2/3 study to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b2 RNA- based vaccine candidates in healthy children, listed as a category 3 study in the RMP.

☒is recommended for approval.

Amendments to the marketing authorisation

The Variation leads to no amendments to the terms of the Community Marketing Authorisation.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Comirnaty-H-C-5735-232586'

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Study C4591048

This report also describes updates to Study C4591048, "A Master Phase 1/2/3 Protocol to Investigate the Safety, Tolerability, and Immunogenicity of Variant-Adapted BNT162b2 RNA-Based Vaccine Candidate(s) in Healthy Children." As detailed in protocol amendment 5 resulted in updates to the study design, primarily for Substudy E.

Study C4591048 is a Phase 1/2/3 master study to investigate the safety, tolerability, and immunogenicity of variant-adapted BNT162b2 RNA-based vaccine candidates. Each substudy, detailed separately in the respective substudy appendix of the master protocol, may be conducted in parallel, as required by the clinical plan.

This report includes the changes in this study described in amendment 5 evaluated via this underlying Type II Variation Procedure. Protocol amendment 5 was predominantly targeted for Substudy E study design and was developed based on feedback from US FDA.

The methodology of Study C4591048 has been assessed during earlier procedure EMEA/H/C/005735/MEA/057 and was considered acceptable.

Clinical data from study C4591048 has previously been evaluated in procedures EMEA/H/C/005735/X/0176/G, EMEA/H/C/005735/II/0177/G and EMEA/H/C/005735/II/0220/G.

Study C4591044

The present submission is intended to provide final immunogenicity and safety analyses 6 months after study vaccination in 940 participants ≥12 years of age who received study vaccination with BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30 µg or 60 µg as Dose 4 after receiving 3 prior doses of original BNT162b2 in Study C4591044 (Cohort 2 and Cohort 3 combined) (Table 1).

Table 1. Summary of Data From C4591044 Cohort 2 and Cohort 2 Combined Provided in this submission

Subset or Cohort[a]	Cohort	Group	Participant Age	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) Dose[b]	Data Summarized
Subset of Cohort 2 and Cohort 3 Combined (Persistence of Response)	2	1	12 through 17 years of age	30 µg	6-month postdose (Dose 4) immunogenicity (Section 2.5.4.1.1)
		2	18 through 55 years of age		
		4	>55 years of age		
	3	1	18 through 55 years of age		
		2	>55 years of age		
Cohort 2 (Variant Neutralization Subset)	2	4	>55 years of age	30 µg	1-month postdose (Dose 4) variant neutralization (Section 2.5.4.1.2)
Cohort 2 (PBMC Subset)	2	2-5	≥18 years of age	30 µg or 60 µg	1-week and 1-,3-, and 6-month postdose (Dose 4) T-cell responses and HLA type (Section 2.5.4.1.3)
Cohort 2 and Cohort 3 Combined	2 and 3	All	12 through 17, 18 through 55, and >55 years of age	30 µg or 60 µg	6-month postdose (Dose 4) safety data (Section 2.5.5.1)

a. Refer to Section 2.5.1.1.1 for further details on study design.
b. Participants received prior doses of original BNT162b2

Study C4591044 was a randomised, active-controlled study to evaluate the safety, tolerability, and immunogenicity of new variant-adapted vaccines. Participants were divided into cohorts to be studied in a staggered or parallel manner. Cohort 2 and Cohort 3 evaluated BNT162b2 Bivalent vaccine that included Original/OMI BA.4-5, in 940 participants ≥12 years of age.

Cohort 2: approximately 500 participants 12 years of age and older who received 3 prior doses of BNT162b2 30-µg received 30 µg or 60 µg of BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) as Dose 4.

- Participants 12 through 17 years of age (Group 1; n=100) received a single 30-µg dose of BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) (open-label).
- Participants 18 through 55 (Groups 2 and 3) and >55 (Groups 4 and 5) years of age (n=100 in each group) were randomised 1:1 within each age group to receive BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) at either 30 or 60 µg (observer-blind).

Cohort 3: approximately 400 participants 18 years of age and older (200 participants 18 through 55 years of age [Group 1] and 200 participants >55 years of age [Group 2]) who received 3 prior doses of BNT162b2 30-µg, received 30 µg of BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) as Dose 4 (open-label).

The 1-months post vaccination data from study C4591044 was assessed during procedure EMEA/H/C/005735/II/0177/G to authorize ORIGINAL/OMI BA.4-.5 among individuals over 12 years of age (15/15 micrograms)/dose and children 5-11 years of age 5/5 micrograms)/dose. Also, the 1-month post-vaccination data was presented in procedures EMEA/H/C/005735/MEA/059-0.59.3. Current submission follows the same study population 3 months and 6 months post vaccination.

6. Study C4591048 Amendment 5

Study C4591048 Substudy E is a Phase 2/3 open-label study to evaluate the safety, tolerability, and immunogenicity of a single age-appropriate dose of BNT162b2 (Omi XBB.1.5) in participants ≥5 to <12 years of age who are COVID-19 vaccine-naïve.

Approximately 300 participants ≥5 to <12 years of age in Group 2 will be enrolled and will receive a single 10-µg dose of BNT162b2 (Omi XBB.1.5). Protocol amendment 5 included the removal of Group 1 (participants ≥2 to <5 years of age) and a change to the comparator group in the immunogenicity analysis.

- The decision was made to not pursue Substudy E Group 1, as this age group (≥2 to <5 years) is being evaluated in Substudy A.
- The comparator group for Substudy E participants ≥5 to ≥12 years of age immunogenicity analysis has been changed from Study C4591007 to Study C4591054 – Substudy A. Study C4591054 –Substudy A has been chosen, as this is a more epidemiologically relevant comparator and allows a more contemporary assessment of hybrid immunity.

Overall Rationale for the Amendment:

This protocol amendment is predominantly targeted at Substudy E. The comparator study for Substudy E participants ≥5 to <12 years of age has been changed from Study C4591007 to Study C4591054 – Substudy A to conduct noninferiority analysis. Study C4591054 – Substudy A has been chosen, as this is a more epidemiologically relevant comparator and allows a more contemporary assessment of hybrid immunity. Additionally, the decision was made to not pursue Substudy E Group 1, as this age group (≥6 months to <2 years) is being evaluated in Substudy A.

Table 2. Protocol Amendment Summary of Changes Table

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
Removed references to Substudy E Group 1	This age group is being evaluated in Substudy A	Throughout
Added section	To clarify the procedure for collecting and storing medical records from participants	Section 10.1.9 Use of Medical Records
Updated the secondary estimand for Substudy A Phase 1	To clarify that GMFRs will be prior to Dose 4	Section 10.7.3 Objectives, Estimands, and Endpoints
Updated the primary and secondary estimands, immunogenicity endpoints, and noninferiority assessments for Substudy A Phase 2/3	In response to feedback from the EMA to allow for analysis by serostatus	Section 10.7.3 Objectives, Estimands, and Endpoints, Section 10.7.9.3.2 Primary Endpoint(s)/Estimand(s) Analysis, and Section 10.7.9.5.1 Immunogenicity Assessment
Updated Substudy E primary and secondary objectives, statistical hypotheses, and the primary, secondary, and tertiary endpoints, estimands, and analyses	To align with the updated comparator for Substudy E	Section 10.11.3 Objectives, Estimands, and Endpoints, Section 10.11.9.1 Statistical Hypotheses, and Section 10.11.9.3 Statistical Analyses
Updated exclusion criteria for Substudy A and updated inclusion and exclusion criteria for Substudy E	To provide guidance on the receipt of concomitant medications	Section 10.7.5.2 Exclusion Criteria, Section 10.11.5.1 Inclusion Criteria, and Section 10.11.5.2 Exclusion Criteria
Removed text regarding administration of a 3-µg dose of study intervention	To align with the removal of Substudy E Group 1	Section 10.11.6.1 Study Intervention(s) Administered
Updated the timing of the statistical analyses for Substudy E	To align with regulatory submission timing	Section 10.11.9.4.1 Analysis Timing
Updated Substudy E immunogenicity assessments	To align with the removal of Substudy E Group 1 and the updated comparator for Substudy E	Section 10.11.9.5 Sample Size Determination
Nonsubstantial Modifications		
Updated the dose selection for Substudy A Phase 2/3 to 10 µg	Following IRC review of Substudy A Phase 1 data, this dose was selected	Throughout
Added the EudraCT number	The EudraCT number was requested and obtained	Section 1.1 Synopsis
Specified which substudies will collect maternal	To clarify that active substudies with participants	Section 6.9 Prior and Concomitant Therapy,

COVID-19 vaccination information	<2 years of age will not be collecting this information, as the impact of maternal vaccination on immune response is difficult to interpret and analyze	Section 10.7.1.3.2.1 Participants ≥6 Months to <2 Years of Age, and Section 10.7.8.5.2.1 Participants ≥6 Months to <2 Years of Age
Added nirsevimab to the list of prohibited medications and clarified that the use of palivizumab is permitted during the study	To provide guidance on the receipt of concomitant medications	Section 6.9.1 Prohibited During the Study and Section 6.9.2 Permitted During the Study
Updated the language for Road-to-Health cards for participants in South Africa	To align with SAPHRA's recommendation	Section 8.11.1 Potential COVID-19/MIS-C Illness Visit (Optimally Within 3 Days After Potential COVID-19 Illness Onset), Section 10.7.8.5.2 Phase 2/3, and Section 10.11.8.5 Substudy E Procedures
Updated the section to replace the emergency contact card with the study information card, and updated Substudy A Phase 2/3 and Substudy E SoAs to include the provision of the study information card	The process of contacting a medically qualified individual has changed	Section 10.1.12 Sponsor's Medically Qualified Individual, Section 10.7.1.3 Schedule of Activities for Substudy A, Section 10.7.8.5.2 Phase 2/3, Section 10.11.1.3 Schedule of Activities for Substudy E, and Section 10.11.8.5 Substudy E Procedures
Updated text to clarify that the participant's parent(s)/legal guardian will receive the nasal self-swab kit	Typographical error	Section 10.7.1.3 Schedule of Activities for Substudy A
Updated Substudy A Phase 2/3 to clarify the procedure for monitoring baseline serostatus	In response to PDCO's request	Section 10.7.4.1 Overall Design
Updated the order of procedures at Visits A201, A301, and A401	To allow the group to be identified prior to study procedures	Section 10.7.8.5.2 Phase 2/3
Removed language to clarify the baseline serostatus of participants	To allow analysis of all participants in the group	Section 10.7.9.1 Statistical Hypotheses
Updated Substudy E procedures to include urine pregnancy testing and confirmation of use of contraception for WOCBP	Participants in Substudy E Group 2 are considered to be WOCBP	Section 10.11.1.3 Schedule of Activities for Substudy E and Section 10.11.8.5 Substudy E Procedures

Table 3. Overview of Substudies A and E after amendment 5

Phase	Enrollment Status at the Time of Protocol Amendment 54	Group	Participant Age	Dose Level	Number of Doses Administered Prior to Enrollment	Dosing Schedule	Number of Doses to Be Administered During the Study	Approximate Number of Participants
Substudy A Phase 1: 3-Dose Series (Bivalent BNT162b2) + Fourth-Dose (BNT162b2 Omi XBB.1.5) Evaluation: Participants ≥6 Months to <4 Years 3 Months of Age								
Phase 1	Complete		Age group 1 (≥6 months to <2 years) and age group 2 (≥2 years to <4 years 3 months)	3 µg	0	Bivalent BNT162b2 at 0, 3, and 11 weeks and BNT162b2 (Omi XBB.1.5) ~6 months after Dose 3	4	60
				6 µg				60
				10 µg				60
Substudy A Phase 2/3: 2-Dose Series BNT162b2 (Omi XBB.1.5) Selected-Dose Evaluation in Participants ≥6 Months to <2 Years of Age and Single-Dose BNT162b2 (Omi XBB.1.5) Selected-Dose Evaluation in Participants ≥2 to <5 Years of Age								
Phase 2/3	~~Not started~~Enrolling	Group 1 – baseline and post–Dose 2 blood draw	Age group 1 (≥6 months to <2 years) 3:1:2 randomization	~~TBD~~10 µg	0	0 and 8 weeks	2	450
		Group 2 – baseline and post–Dose 1 blood draw		~~TBD~~ 10 µg		0 and 8 weeks	2	150
		Group 3 – baseline and post–Dose 3 blood draw		3 µg		0, 3, and 11 weeks	3	300
Phase 2/3	~~Not started~~ Complete	Group 4 – baseline and post–Dose 1 blood draw	Age group 2 (≥2 to <5 years) 3:1 randomization	~~TBD~~ 10 µg	0		1	450
		Group 5 – no blood draw		~~TBD~~ 10 µg				150
Substudy E: Single Age-Appropriate Dose BNT162b2 (Omi XBB.1.5) Evaluation: ~~Participants ≥2 to <5 Years of Age (Group 1)~~, Participants ≥5 to <12 Years of Age (Group 2)								
Phase 2/3	~~Not started~~Complete	~~Group 1~~	~~≥2 to <5 years~~	~~3 µg~~	0		~~1~~	~~100~~
		Group 2	≥5 to <12 years	10 µg			1	300

Assessor´s comment: the amendments are justified and no loss of information is expected due to the removal of the Substudy E, Group 1 as this age and dose group is covered in Substudy A Phase 1. The amendments are therefore acceptable.

7. Clinical Efficacy aspects

7.1. Methods – analysis of data submitted, Study C4591044

Table 4. Cohort 2 Design

Cohort 2: BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5)						
Group	**Participant Age Group**	**Prior Doses of BNT162b2**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomisation / Blind**
1	12-17 years	3	150-365 days	30 µg	100	Open label
2	18-55 years	3	150-365 days	30 µg	100	Randomize 1:1 Observer-blind
3	18-55 years	3	150-365 days	60 µg	100	
4	>55 years	3	150-365 days	30 µg	100	Randomize 1:1 Observer-blind
5	>55 years	3	150-365 days	60 µg	100	

Table 5. Cohort 3 Design

Cohort 3: BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5)						
Group	**Participant Age Group**	**Prior Doses of BNT162b2**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomisation / Blind**

1	18-55 years	3	150-365 days	30 µg	200	Open label
2	>55 years	3	150-365 days	30 µg	200	Open label

Note: For certain safety and immunogenicity objectives, the 18- through 55-age group and the >55-age group will comprise participants from Cohorts 2 and 3 combined.

Table 6. Exploratory immunogenicity objectives, estimands and endpoints of study C4591044

Objectives/estimands/endpoints to be reported later are in gray shading and/or **bold**

Objectives	Estimands	Endpoints	Reference
Cohort 2/Group 1, Cohort 2/Group 2 + Cohort 3/Group 1 combined,[f] Cohort 2/Group 4 + Cohort 3/Group 2 combined,[f] Cohort 2/Group 3, and Cohort 2/Group 5[h]: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg compared to BNT162b2 30 µg[f] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): At baseline and 1 month, 3 months, and 6 months after study vaccination, • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[b] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[c]–neutralizing titers	Data are reported in this CSR
Cohort 1, Cohort 2 + Cohort 3 combined, **Cohort 4:** To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases	Data through 1 month after study vaccination for Cohort 2 and Cohort 3 combined are reported in the 1-month analysis interim CSR dated 03 February 2023
			Data through 6 Month after study vaccination for Cohort 2 and Cohort 3 combined are reported in this CSR **Data for Cohort 1 and Cohort 4 will be reported at a later time**
Cohort 1, Cohort 2 + Cohort 3 combined, Cohort 4: To describe the immune response to other emerging variants (under monitoring, of interest, and/or of concern).		• **SARS-CoV-2–neutralizing titers for other variants (under monitoring, of interest, and/or of concern) not already specified**	BA.4.6, BA.2.75.2, BQ.1.1, and XBB neutralization data before and at 1 month after study vaccination for a subset of Cohort 2 participants are reported in the 1-month analysis interim CSR dated 03 February 2023 XBB.1.5, XBB.1.16, and CH.1.1 neutralization data before and at 1 month after study vaccination for a subset of Cohort 2 participants are reported in this CSR
			Cohort 1 data will be reported at a later time
Cohort 2: To describe the cell-mediated immune response, **and additional humoral immune response** parameters, to the reference strain[c] and Omicron in a subset of participants with PBMC samples collected.			Data are reported in this CSR **These data will be reported at a later time**

b. Seroresponse is defined as achieving a ≥4-fold rise from the baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
c. Reference strain is also referred to as the Original, Wild Type, or ancestral strain (Wuhan-Hu-1; USA-WA1/2020).
f. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) from C4591044 Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg and from the C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be selected for this objective. The subset selected will include a similar percentage of participants with baseline positive SARS-CoV-2 infection status whenever feasible. Comparisons to the immune response elicited by BNT162b2 30 µg (subset of participants from the C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose) were not completed for the exploratory objective describing the immune response at the 3-month and 6-month timepoints because it was deemed unnecessary to repeat this analysis for the same timepoints, particularly since the monovalent BNT162b2 was no longer authorized for use in the US.
h. Immunogenicity analyses at later timepoints for the 60 µg dose groups were not performed as part of the exploratory objectives because the immunogenicity and safety data up to 1 month after vaccination indicated that the 30-µg dose had a favorable benefit risk profile in this population further supporting the authorized 30-µg dose.
Source: Appendix 16.1.1, Protocol Section 3

Immunogenicity

Immunogenicity results were based on validated assays for 50% SARS-CoV-2 neutralizing titres on a newly developed 384-well assay platform (reference strain [USA-WA1/2020, isolated in January 2020], and Omicron BA.4/BA.5) at before first study vaccination (Dose 4) and 1 month after study vaccination (Dose 4) with the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg for participants enrolled in this study, and reported as GMTs, percentages/difference in percentages with seroresponse, and GMFRs.

A non-validated FFRNT was used to determine Omicron-specific and reference strain neutralizing titres among a subset of BNT162b2-experienced participants 18 through 55 and/or >55 years of age who received a booster (Dose 4) of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in C4591044 Cohort 2 and BNT162b2-experienced adults >55 years of age who received a booster (Dose 4) of BNT162b2 30 µg in C4591031 Substudy E.

Note that the selection of participants from C4591031 Substudy E intentionally included similar proportions of individuals without evidence of prior SARS-CoV-2 infection balanced with those who had evidence of prior SARS-CoV-2 infection.

Assessor´s comment: The aims of the currently presented exploratory immunogenicity analysis were to follow up the antibody persistance over 3 and 6 months post vaccination, to explore cross-neutralizing antibodies to other newly circulating omicron variants and describe the cell- mediated immunity after the vaccination with bivalent original/Omicron BA.4-5 vaccine. The analyses were descriptive, which was agreed to earlier. The methodology of this study has been assessed during earlier procedures, found to be acceptable and therefore it is not repeated here again.

The Applicant stated, that they have submitted final report for C4591044, but it seems, that more data for Cohorts 1, 2, 3 and 4 may be coming. The MAH has clarified that they do not intend to submit further supplementary clinical study reports unless benefit/risk profile changes, which is acceptable from CHMP side.

7.2. Results

7.2.1. Immunogenicity populations

Subset of BNT162b2 Bivalent 30 µg Groups of Cohort 2 and Cohort 3 Combined (Persistence of Response)

This part of the immunogenicity analysis included all participants in Cohort 2/Group 1 (12 through 17 years of age) and subsets of approximately 100 participants in Cohort 2/Group 2 + Cohort 3/Group 1 combined (18 through 55 years of age) and Cohort 2/Group 4 + Cohort 3/Group 2 combined (>55 years of age) who received BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30 µg.

For participants 18 through 55 and >55 years of age, 50 participants who were baseline positive and baseline negative in each age group were randomly selected from participants who met other evaluability criteria and had sufficient blood volume at each timepoint.

Evaluable Immunogenicity Population

The evaluable immunogenicity population consisted of 104 participants (97.2%), 100 participants (100.0%), and 100 participants (100.0%) who were 12 through 17 years of age, 18 through 55 years of age, and >55 years of age, respectively. There were 25 participants (23.4%), 50 participants (50.0%), and 50 participants (50.0%) who were 12 through 17 years of age, 18 through 55 years of age, and >55 years of age, respectively, without evidence of infection up to 1 month after study vaccination. Three participants (2.8%) 12 through 17 years of age were excluded from the evaluable immunogenicity population and the most common reason was "did not have at least 1 valid and determinate immunogenicity result within 28-42 days after the study vaccination".

3-Month Evaluable Immunogenicity Population

The 3-month evaluable immunogenicity population consisted of 100 participants from each age group. There were 19 participants (17.8%), 47 participants (47.0%), and 45 participants (45.0%) who were 12 through 17 years of age, 18 through 55 years of age, and >55 years of age, respectively, without evidence of infection up to 3 months after study vaccination. Seven participants (6.5%) 12 through 17 years of age were excluded from the evaluable immunogenicity population and the most common reason was "did not have at least 1 valid and determinate immunogenicity result at the 3-month post-study vaccination visit".

6-Month Evaluable Immunogenicity Population

The 6-month evaluable immunogenicity population consisted of 98 participants (91.6%) who were 12 through 17 years of age, and 100 participants (100.0%) who were 18 through 55 years of age and >55 years of age, each. Of these participants, there were 10 participants (9.3%), 37 participants (37.0%), and 41 participants (41.0%) who were 12 through 17 years of age, 18 through 55 years of age, and >55 years of age, respectively, without evidence of infection up to 6 months after study vaccination. Nine participants (8.4%) 12 through 17 years of age were excluded from the evaluable immunogenicity population and the most common reason was "did not have at least 1 valid and determinate immunogenicity result at the 6-month post-study vaccination visit".

Neutralization of Variants in Cohort 2 Subset

Omicron XBB.1.5

The descriptive neutralization immunogenicity analysis subset included approximately 40 randomised participants per vaccine group. Subsets were selected from participants >55 years of age in C4591044 Cohort 2 who received BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30 µg (Group 4) and participants >55 years of age group in C4591031 Substudy E Expanded Cohort who received BNT162b2 30 µg. Note that the selection of participants intentionally included similar proportions of individuals without evidence of prior SARS-CoV-2 infection balanced with those who had evidence of prior SARS-CoV-2 infection.

Omicron XBB.1.16 and Omicron CH.1.1

The descriptive new variant neutralization immunogenicity analysis subset for Omicron XBB.1.16 and Omicron CH.1.1 was the same subset described in Section above.

T-cell Responses in PBMC Subset (Cohort 2)

For participants ≥18 years of age in Cohort 2, the cell-mediated immune response and additional humoral immune response parameters to the reference strain and Omicron strain (BA.4/BA.5) were summarised at each time point for the subset of participants with PBMC samples collected in each group. All participants who consented to PBMC isolation and HLA typing in Cohort 2 were included in the analysis.

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, the evaluable immunogenicity population consisted of 20 participants (80.0%) 18 through 55 years of age and 20 participants (83.3%) >55 years of age.

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, the evaluable immunogenicity population consisted of 28 participants (93.3%) 18 through 55 years of age and 16 participants (100.0%) >55 years of age.

7.2.2. Exploratory Immunogenicity Analyses

Immunogenicity

Persistence of Response in Subset of BNT162b2 Bivalent 30 µg Groups of Cohort 2 and Cohort 3 Combined

Geometric Mean Titres

Omicron BA.4/BA.5 Neutralization

Participants With or Without Evidence of Infection

Omicron BA.4/BA.5 GMTs at prevaccination and 1, 3 and 6 months after study vaccination were higher for participants who had evidence of prior SARS-CoV-2 infection at baseline (baseline positive) compared with those who were without evidence of prior SARS-CoV-2 infection (baseline negative).

Within baseline positive and baseline negative groups, Omicron BA.4/BA.5 neutralizing GMTs at prevaccination and 1, 3 and 6 months after study vaccination were higher in participants 12 through 17 years of age.

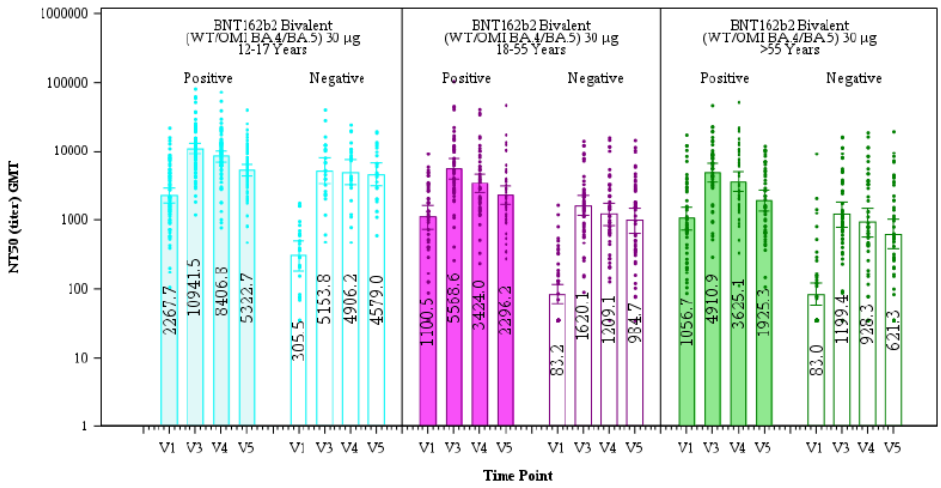
Across all age groups within baseline positive and baseline negative groups, Omicron BA.4/BA.5 neutralizing GMTs were observed to be highest at 1 month after study vaccination and gradually decreased at 3 and 6 months after study vaccination. However, at the 6-month timepoint, GMTs were still considerably higher than the baseline value across all age groups.

Results for participants with or without evidence of infection in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Participants Without Evidence of Infection

Observed Omicron BA.4/BA.5 neutralizing GMTs at prevaccination and 1, 3 and 6 months after study vaccination were higher for participants 12 to 17 compared to participants 18 through 55 years of age and >55 years of age. Within the age group of 12 to 17 years of age, GMTs were generally similar at 1, 3, and 6 months after study vaccination. Within the age groups of 18 through 55 years of age and >55 years of age, Omicron BA.4/BA.5 neutralizing GMTs were observed to be highest at 1 month after study vaccination and gradually decreased at 3 and 6 months after study vaccination. However, at the 6-month timepoint, GMTs were still considerably higher than the baseline value across all age groups.

Figure 1. GMTs and 95% CIs, by Baseline SARS-CoV-2 Status: Omicron BA.4/BA.5 – NT50 – Subset of BNT162b2 Bivalent 30-µg Groups of Cohort 2 and Cohort 3 Combined – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: V1 = Prevaccination; V3 = 1 Month after vaccination; V4 = 3 Months after vaccination; V5 = 6 Months after vaccination.
Note: All participants in Cohort 2/Group 1 and a subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) from Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg as a second booster dose were selected for the analysis.
Note: All samples were analyzed contemporaneously.
Note: Dots represent individual antibody levels. Number within each bar denotes geometric mean.
Note: Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
Note: Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
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Output File: /nda2_ub1044/C4591044_C23_6MPD_IMM/adva_f002_bs_6m_ba4_gmt50_c23

Table 7. Geometric Mean Titres, by Baseline SARS-CoV-2 Status – Subset of BNT162b2 Bivalent 30-µg Groups of Cohort 2 and Cohort 3 Combined – Participants With or Without Evidence of Infection Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			BNT162b2 Bivalent (WT/OMI BA.4/BA.5)					
			12-17 Years		18-55 Years		>55 Years	
			30 µg		30 µg		30 µg	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	All	Prevax	104	1373.8 (1043.6, 1808.6)	100	302.5 (210.6, 434.6)	100	296.1 (205.2, 427.4)
		1 Month	104	9064.4 (7558.6, 10870.2)	100	3003.6 (2307.3, 3909.9)	100	2427.0 (1811.4, 3251.8)
		3 Months	100	7347.8 (6108.3, 8838.9)	100	2034.7 (1564.8, 2645.7)	100	1834.4 (1333.7, 2523.2)
		6 Months	98	5122.2 (4335.4, 6051.8)	100	1503.7 (1150.7, 1964.9)	100	1093.7 (798.4, 1498.4)
	Positive[d]	Prevax	78	2267.7 (1780.8, 2887.8)	50	1100.5 (735.2, 1647.5)	50	1056.7 (717.7, 1555.8)
		1 Month	78	10941.5 (9119.4, 13127.7)	50	5568.6 (3997.4, 7757.5)	50	4910.9 (3623.7, 6655.2)
		3 Months	75	8406.8 (6892.0, 10254.6)	50	3424.0 (2505.1, 4679.9)	50	3625.1 (2590.6, 5072.7)
		6 Months	73	5322.7 (4420.8, 6408.5)	50	2296.2 (1707.6, 3087.7)	50	1925.3 (1375.0, 2696.0)
	Negative[e]	Prevax	26	305.5 (184.4, 505.9)	50	83.2 (60.0, 115.2)	50	83.0 (57.0, 120.9)
		1 Month	26	5153.8 (3346.7, 7936.7)	50	1620.1 (1153.2, 2275.9)	50	1199.4 (784.3, 1834.3)
		3 Months	25	4906.2 (3213.6, 7490.1)	50	1209.1 (827.8, 1766.0)	50	928.3 (573.6, 1502.4)
		6 Months	25	4579.0 (3109.3, 6743.3)	50	984.7 (644.7, 1504.0)	50	621.3 (378.9, 1018.9)

Reference Strain Neutralization

Participants With or Without Evidence of Infection

Similar to Omicron BA.4/BA.5 neutralizing GMTs, reference strain GMTs at prevaccination and 1,3, and 6 months after study vaccination were higher for participants who were baseline positive compared with those who were baseline negative for SARS-CoV-2.

Within baseline positive and baseline negative groups, reference strain neutralizing GMTs at prevaccination and 1, 3 and 6 months after study vaccination were higher in participants 12 through 17 years of age and generally similar for participants 18 through 55 years of age and participants >55 years of age. Across all age groups within baseline positive and baseline negative groups, reference strain neutralizing GMTs were observed to be highest at 1 month after study vaccination and gradually decreased at 3 and 6 months after study vaccination. Within baseline negative groups at the 6-month timepoint, GMTs were still considerably higher than the baseline value across all age groups.

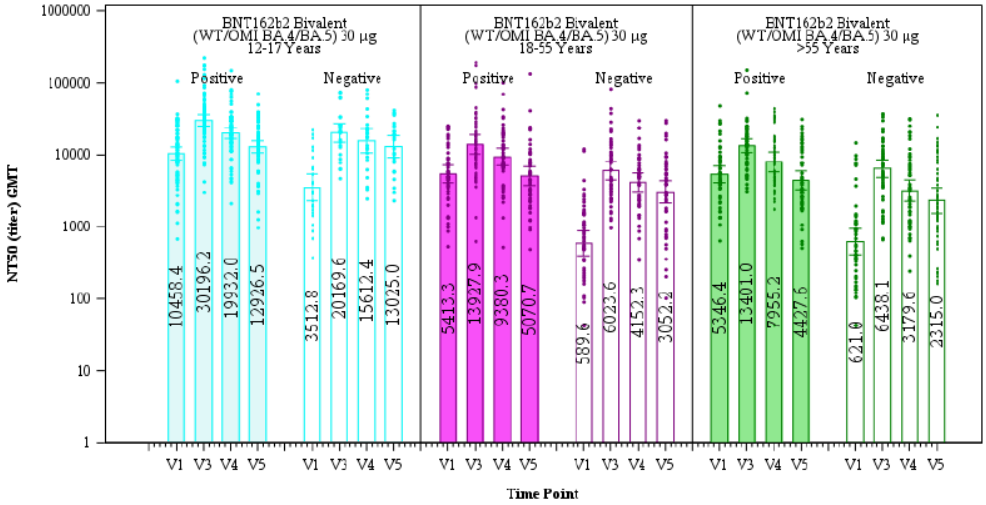
Results for participants with or without evidence of infection in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Participants Without Evidence of Infection

Similar to Omicron BA.4/BA.5 neutralizing GMTs, reference strain neutralizing GMTs at prevaccination and 1, 3 and 6 months after study vaccination were substantially higher for participants 12 to 17 compared to participants 18 through 55 years of age and >55 years of age and generally similar for participants 18 through 55 years of age and participants >55 years of age. Within the age group of 12 to 17 years of age, GMTs were similar at 3 and 6 months after study vaccination.

Within the age groups of 18 through 55 years of age and >55 years of age, reference strain neutralizing GMTs were observed to be highest at 1 month after study vaccination and gradually decreased at 3 and 6 months after study vaccination. However, at the 6-month timepoint, GMTs were still considerably higher than the baseline value across all age groups.

Figure 2. Figure 3. GMTs and 95% CIs, by Baseline SARS-CoV-2 Status: Reference Strain – NT50 – Subset of BNT162b2 Bivalent 30- µg Groups of Cohort 2 and Cohort 3 Combined – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: V1 = Prevaccination; V3 = 1 Month after vaccination; V4 = 3 Months after vaccination; V5 = 6 Months after vaccination.

Note: All participants in Cohort 2/Group 1 and a subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) from Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg as a second booster dose were selected for the analysis.

Note: All samples were analyzed contemporaneously.

Note: Dots represent individual antibody levels. Number within each bar denotes geometric mean.

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

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

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Output File: ./nda2_ub1044/C4591044_C23_6MPD_IMM/adva_f002_bs_6m_wt_gmt50_c23

Table 8. Geometric Mean Titres, by Baseline SARS-CoV-2 Status – Subset of BNT162b2 Bivalent 30-µg Groups of Cohort 2 and Cohort 3 Combined – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			BNT162b2 Bivalent (WT/OMI BA.4/BA.5)					
			12-17 Years		18-55 Years		>55 Years	
			30 µg		30 µg		30 µg	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	All	Prevax	104	7961.8 (6475.7, 9788.9)	100	1786.5 (1290.0, 2474.1)	100	1822.1 (1319.7, 2515.7)
		1 Month	104	27298.5 (23313.9, 31964.1)	100	9159.4 (7317.0, 11465.9)	100	9288.5 (7683.2, 11229.3)
		3 Months	100	18751.3 (15980.2, 22002.8)	100	6241.0 (5031.4, 7741.4)	100	5029.4 (3922.4, 6448.7)
		6 Months	98	12951.6 (10994.8, 15256.6)	100	3934.1 (3106.6, 4982.0)	99	3191.1 (2465.8, 4129.7)
	Positive[d]	Prevax	78	10458.4 (8507.2, 12857.0)	50	5413.3 (4085.1, 7173.4)	50	5346.4 (4104.9, 6963.4)
		1 Month	78	30196.2 (25154.5, 36248.3)	50	13927.9 (10257.8, 18911.1)	50	13401.0 (10819.4, 16598.5)
		3 Months	75	19932.0 (16735.7, 23738.8)	50	9380.3 (7097.7, 12396.9)	50	7955.2 (5776.7, 10955.3)
		6 Months	73	12926.5 (10688.1, 15633.7)	50	5070.7 (3749.0, 6858.3)	49	4427.6 (3290.2, 5958.2)
	Negative[e]	Prevax	26	3512.8 (2283.1, 5404.9)	50	589.6 (396.4, 876.9)	50	621.0 (410.9, 938.3)
		1 Month	26	20169.6 (14896.1, 27310.1)	50	6023.6 (4488.3, 8084.0)	50	6438.1 (4841.0, 8562.1)
		3 Months	25	15612.4 (10663.2, 22858.7)	50	4152.3 (3090.2, 5579.3)	50	3179.6 (2251.7, 4489.9)
		6 Months	25	13025.0 (9209.7, 18420.9)	50	3052.2 (2130.3, 4373.2)	50	2315.0 (1536.1, 3489.1)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants in Cohort 2/Group 1 and a subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) from Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg as a second booster dose were selected for the analysis.
Note: All samples were analyzed contemporaneously.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
PFIZER CONFIDENTIAL SDTM Creation: 28MAR2024 (11:17) Source Data: adva Table Generation: 01APR2024 (04:41)
(Database snapshot date: 21SEP2023) Output File: ./nda2_ub1044/C4591044_C23_6MPD_IMM/adva_s001_gmt_bs_6m_evl_c23

Geometric Mean Fold Rises

Omicron BA.4/BA.5 Neutralization

Participants With or Without Evidence of Infection

Omicron BA.4/BA.5 GMFRs from before study vaccination to 1, 3 and 6 months after study vaccination were higher for participants who were baseline negative compared with those who were baseline positive for SARS-CoV-2.

Within participants who were baseline negative, GMFRs remained high up to 6 months after study vaccination across all age groups, and highest in 12 through 17 years of age.

Within baseline positive or baseline negative groups, GMFRs from before study vaccination to 1, 3 and 6 months after study vaccination were generally similar for all age groups. GMFRs were highest at 1 month and gradually decreased at 3 and 6 months after study vaccination. However, GMFRs remained high up to 6 months after study vaccination across all age groups, particularly within baseline negative groups.

Results for participants with or without evidence of infection in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Participants Without Evidence of Infection

Overall, in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, GMFRs of neutralizing titres from before study vaccination to 1, 3 and 6 months after study vaccination for Omicron BA.4/BA.5 were generally similar across all age groups. Across all age groups, GMFRs were highest at 1 month and gradually decreased at 3 and 6 months after study vaccination. However, GMFRs remained high up to 6 months after study vaccination across all age groups.

Reference Strain Neutralization

Participants With or Without Evidence of Infection

Similar to Omicron BA.4/BA.5 GMFRs, reference strain GMFRs from before study vaccination to 1, 3 and 6 months after study vaccination were higher for participants who were baseline negative compared with those who were baseline positive for SARS-CoV-2.

Within baseline positive or baseline negative groups, GMFRs from before study vaccination to 1, 3 and 6 months after study vaccination were similar for all age groups. GMFRs were highest at 1 month and gradually decreased at 3 and 6 months after study vaccination. However, GMFRs remained high at 6 months after study vaccination across all age groups within baseline negative groups.

Results for participants with or without evidence of infection in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Participants Without Evidence of Infection

Similar to Omicron BA.4/BA.5 GMFRs in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, GMFRs of neutralizing titres from before study vaccination to 1, 3 and 6 months after study vaccination for the reference strain were similar across all age groups. Across all age groups, GMFRs were highest at 1 month and gradually decreased at 3 and 6 months after study vaccination. However, GMFRs remained high up to 6 months after study vaccination across all age groups.

Table 9. Geometric Mean Fold Rises From Before the Study Vaccination to Each Subsequent Time Point, by Baseline SARS-CoV-2 Status – Subset of BNT162b2 Bivalent 30-µg Groups of Cohort 2 and Cohort 3 Combined – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			BNT162b2 Bivalent (WT/OMI BA.4/BA.5)					
			12-17 Years		18-55 Years		>55 Years	
			30 µg		30 µg		30 µg	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	All	1 Month	104	6.6 (5.4, 8.1)	100	9.9 (7.4, 13.3)	100	8.2 (6.2, 10.9)
		3 Months	100	5.4 (4.3, 6.8)	100	6.7 (5.1, 8.9)	100	6.2 (4.6, 8.4)
		6 Months	98	3.8 (2.9, 4.8)	100	5.0 (3.5, 7.0)	100	3.7 (2.7, 5.1)
	Positive[d]	1 Month	78	4.8 (3.9, 5.9)	50	5.1 (3.4, 7.6)	50	4.6 (3.2, 6.7)
		3 Months	75	3.8 (3.0, 4.7)	50	3.1 (2.2, 4.4)	50	3.4 (2.3, 5.0)
		6 Months	73	2.3 (1.9, 3.0)	50	2.1 (1.4, 3.1)	50	1.8 (1.2, 2.7)
	Negative[e]	1 Month	26	16.9 (11.6, 24.5)	50	19.5 (13.9, 27.3)	50	14.5 (9.9, 21.2)
		3 Months	25	16.2 (10.9, 24.0)	50	14.5 (10.3, 20.6)	50	11.2 (7.4, 17.0)
		6 Months	25	15.1 (10.6, 21.5)	50	11.8 (7.7, 18.3)	50	7.5 (4.8, 11.7)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	All	1 Month	104	3.4 (2.9, 4.0)	100	5.1 (3.9, 6.7)	100	5.1 (4.0, 6.5)
		3 Months	100	2.4 (2.0, 2.8)	100	3.5 (2.7, 4.5)	100	2.8 (2.2, 3.5)
		6 Months	98	1.6 (1.4, 1.9)	100	2.2 (1.6, 3.0)	99	1.7 (1.3, 2.3)
	Positive[d]	1 Month	78	2.9 (2.4, 3.4)	50	2.6 (1.9, 3.5)	50	2.5 (1.9, 3.2)
		3 Months	75	1.9 (1.6, 2.3)	50	1.7 (1.3, 2.3)	50	1.5 (1.1, 2.0)
		6 Months	73	1.2 (1.0, 1.4)	50	0.9 (0.7, 1.3)	49	0.8 (0.6, 1.1)
	Negative[e]	1 Month	26	5.7 (4.0, 8.2)	50	10.2 (7.2, 14.4)	50	10.4 (7.6, 14.2)
		3 Months	25	4.6 (3.1, 6.7)	50	7.0 (5.1, 9.8)	50	5.1 (3.8, 6.9)
		6 Months	25	3.8 (2.8, 5.2)	50	5.2 (3.4, 7.9)	50	3.7 (2.5, 5.5)

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All participants in Cohort 2/Group 1 and a subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) from Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg as a second booster dose were selected for the analysis.

Note: All samples were analyzed contemporaneously.

a. Protocol-specified timing for blood sample collection.

b. n = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point.

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

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

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

PFIZER CONFIDENTIAL SDTM Creation: 28MAR2024 (11:17) Source Data: adva Table Generation: 01APR2024 (04:41)
(Database snapshot date: 21SEP2023) Output File: ./nda2_ub1044/C4591044_C23_6MPD_IMM/adva_s001_gmfr_6m_evl_c23

Seroresponse

Omicron BA.4/BA.5 Neutralization

Participants With or Without Evidence of Infection

Across all age groups, seroresponse rates at 1,3 and 6 months after study vaccination were generally higher for participants who were baseline negative compared to those who were baseline positive for SARS-CoV-2.

Within baseline positive and baseline negative groups, seroresponse rates were generally similar across all age groups at 1,3, and 6 months after study vaccination. Seroresponse rates remained high at 6 months after study vaccination across all age groups, particularly within baseline negative groups.

Results for participants with or without evidence of infection in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Participants Without Evidence of Infection

In the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the proportion of participants who achieved a seroresponse to Omicron BA.4/BA.5 at 1 and 3 months after study vaccination was generally similar for all age groups. At 6 months after study vaccination, seroresponse rate was highest in participants 12 through 17 years of age, followed by participants 18 through 55 years of age. Overall, seroresponse rates remained high at 6 months after study vaccination across all age groups.

Reference Strain Neutralization

Participants With or Without Evidence of Infection

Similar to Omicron BA.4/BA.5 seroresponse rates, across all age groups, seroresponse rates to the reference strain at 1,3 and 6 months after study vaccination were generally higher for participants who were baseline negative compared to those who were baseline positive for SARS-CoV-2.

Within baseline positive and baseline negative groups, seroresponse rates to the reference strain were similar at 1,3, and 6 months after study vaccination in participants 18 through 55 and participants >55 years of age. Within baseline positive and baseline negative groups, the observed proportion of participants 12 through 17 years of age achieving seroresponse to the reference strain was similar or slightly lower at 1, 3, and 6 months after study vaccination compared to participants 18 through 55 and participants >55 years of age. Seroresponse rates remained high at 6 months after study vaccination across all age groups, within baseline negative groups.

Results for participants with or without evidence of infection in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Participants Without Evidence of Infection

In the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the proportion of participants who achieved a seroresponse to the reference strain at 1,3 and 6 months after study vaccination was generally similar for all age groups. Overall, seroresponse rates remained high at 6 months after study vaccination across all age groups.

Table 10. Number (%) of Participants Achieving Seroresponse, by Baseline SARS-CoV-2 Status – Subset of BNT162b2 Bivalent 30-µg Groups of Cohort 2 and Cohort 3 Combined – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			BNT162b2 Bivalent (WT/OMI BA.4/BA.5)					
			12-17 Years		18-55 Years		>55 Years	
			30 µg		30 µg		30 µg	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	All	1 Month	104	68 (65.4) (55.4, 74.4)	100	69 (69.0) (59.0, 77.9)	100	64 (64.0) (53.8, 73.4)
		3 Months	100	58 (58.0) (47.7, 67.8)	100	54 (54.0) (43.7, 64.0)	100	54 (54.0) (43.7, 64.0)
		6 Months	98	46 (46.9) (36.8, 57.3)	100	46 (46.0) (36.0, 56.3)	100	36 (36.0) (26.6, 46.2)
	Positive[e]	1 Month	78	44 (56.4) (44.7, 67.6)	50	26 (52.0) (37.4, 66.3)	50	25 (50.0) (35.5, 64.5)
		3 Months	75	34 (45.3) (33.8, 57.3)	50	18 (36.0) (22.9, 50.8)	50	20 (40.0) (26.4, 54.8)
		6 Months	73	22 (30.1) (19.9, 42.0)	50	11 (22.0) (11.5, 36.0)	50	11 (22.0) (11.5, 36.0)
	Negative[f]	1 Month	26	24 (92.3) (74.9, 99.1)	50	43 (86.0) (73.3, 94.2)	50	39 (78.0) (64.0, 88.5)
		3 Months	25	24 (96.0) (79.6, 99.9)	50	36 (72.0) (57.5, 83.8)	50	34 (68.0) (53.3, 80.5)
		6 Months	25	24 (96.0) (79.6, 99.9)	50	35 (70.0) (55.4, 82.1)	50	25 (50.0) (35.5, 64.5)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	All	1 Month	104	42 (40.4) (30.9, 50.5)	100	55 (55.0) (44.7, 65.0)	100	53 (53.0) (42.8, 63.1)
		3 Months	100	26 (26.0) (17.7, 35.7)	100	41 (41.0) (31.3, 51.3)	100	35 (35.0) (25.7, 45.2)
		6 Months	98	16 (16.3) (9.6, 25.2)	100	30 (30.0) (21.2, 40.0)	99	21 (21.2) (13.6, 30.6)
	Positive[e]	1 Month	78	23 (29.5) (19.7, 40.9)	50	16 (32.0) (19.5, 46.7)	50	13 (26.0) (14.6, 40.3)
		3 Months	75	12 (16.0) (8.6, 26.3)	50	9 (18.0) (8.6, 31.4)	50	5 (10.0) (3.3, 21.8)
		6 Months	73	4 (5.5) (1.5, 13.4)	50	7 (14.0) (5.8, 26.7)	49	4 (8.2) (2.3, 19.6)
	Negative[f]	1 Month	26	19 (73.1) (52.2, 88.4)	50	39 (78.0) (64.0, 88.5)	50	40 (80.0) (66.3, 90.0)
		3 Months	25	14 (56.0) (34.9, 75.6)	50	32 (64.0) (49.2, 77.1)	50	30 (60.0) (45.2, 73.6)
		6 Months	25	12 (48.0) (27.8, 68.7)	50	23 (46.0) (31.8, 60.7)	50	17 (34.0) (21.2, 48.8)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants in Cohort 2/Group 1 and a subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) from Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg as a second booster dose were selected for the analysis.
Note: All samples were analyzed contemporaneously.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
f. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Assessor´s comment: The persistent antibody level was observed up to 6 months post vaccination in all age groups regardless of the baseline COVID-19 experience status. The adolescent group demonstrated higher neutralizing antibody levels than adults and older adults as expected. All participants had high a level of neutralizing antibodies against wt strain at the baseline due to the recent vaccination (less than 1 year ago) with Original vaccine. The seroresponse rate, defined as percentage of participants achieving a ≥4-fold rise from baseline (before the study vaccination) at each timepoint after vaccination (or postvaccination assay result ≥4 × LLOQ if the baseline measurement was below LLOQ), depends of the baseline antibody level. If the baseline antibody level is already high, it is not biologically possible to reach 4 fold rise after the vaccination. Therefore seroresponse rate is not very informative in case of booster vaccination.

Neutralization of Variants in Cohort 2 Subset

Geometric Mean Titres

Omicron XBB.1.5 Neutralization

Participants With or Without Evidence of Infection

Among participants in the evaluable immunogenicity population with or without evidence of prior SARS-CoV-2 infection up to 1 month after the study vaccination (all participants): The observed GMTs at 1-month postdose against Omicron variant XBB.1.5 were higher in the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg group compared to the BNT162b2 30-µg group for all participants and within the baseline positive and baseline negative groups.

Among both vaccine groups in the evaluable immunogenicity population, GMTs (against XBB.1.5 or against BA.4/BA.5) at predose and 1-month postdose were higher for participants with evidence of prior SARS-CoV-2 infection at baseline (baseline positive) compared with those without evidence of prior SARS-CoV-2 infection at baseline (baseline negative).

Similar results were observed for participants with or without evidence of prior SARS-CoV-2 infection in the all-available immunogenicity population.

Participants Without Evidence of Infection

Among participants in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection up to 1 month after the study vaccination:

- The observed GMTs at 1-month postdose against Omicron XBB.1.5 were higher in the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg group compared to the BNT162b2 30-µg group.
- Despite different intervals from dose 3 to 4, the pre-dose 4 neutralizing titres against Omicron XBB.1.5 were similar for the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg and BNT162b2 30-µg vaccine groups.

Table 11. Geometric Mean Titres, by Baseline SARS-CoV-2 Status – XBB.1.5 Neutralization – Subset of Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Participants >55 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		C4591031 BNT162b2 30 µg	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron XBB.1.5 - NT50 (titer)	All	Prevax	36	18.3 (13.2, 25.5)	40	32.5 (21.1, 49.9)
		1 Month	36	111.0 (72.2, 170.7)	40	47.6 (30.2, 74.9)
	Positive[d]	Prevax	19	27.3 (15.9, 46.8)	20	72.1 (37.9, 137.1)
		1 Month	19	162.9 (93.0, 285.5)	20	117.1 (62.0, 221.2)
	Negative[e]	Prevax	17	11.8 (9.0, 15.4)	20	14.6 (10.6, 20.2)
		1 Month	17	72.2 (37.3, 139.8)	20	19.3 (13.5, 27.6)
SARS-CoV-2 FFRNT - Omicron BA.4/BA.5 - NT50 (titer)	All	Prevax	36	93.3 (52.7, 165.4)	40	134.5 (74.7, 242.3)
		1 Month	36	1076.3 (695.6, 1665.4)	40	309.1 (191.8, 498.2)
	Positive[d]	Prevax	19	303.0 (167.9, 546.5)	20	400.9 (190.0, 845.7)
		1 Month	19	1843.5 (1108.4, 3066.1)	20	889.5 (498.1, 1588.8)
	Negative[e]	Prevax	17	25.0 (14.7, 42.7)	20	45.2 (23.7, 85.9)
		1 Month	17	589.9 (304.2, 1144.0)	20	107.4 (72.9, 158.3)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Approximately forty participants (20 baseline SARS-CoV-2 positive status and 20 negative status) were selected from >55 years age group in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and from Study C4591031 Substudy E expanded cohort (>55 years) BNT162b2 30-µg group.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 17JAN2023 (02:16)
(Data cutoff date : C4591044 [12OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C2_XBBCMB/adva_s001_gmt_bs_xbb_evl_c2

Omicron XBB.1.16 and Omicron CH.1.1 Neutralization

Participants With or Without Evidence of Infection

Among participants in the evaluable immunogenicity population with or without evidence of prior SARS-CoV-2 infection up to 1 month after the study vaccination (all participants): The observed GMTs at 1-month post dose against Omicron variant XBB.1.16 and Omicron variant CH.1.1 were higher in the

BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg group compared to the BNT162b2 30-µg group for all participants and within the baseline positive and baseline negative groups.

Among both vaccine groups in the evaluable immunogenicity population, GMTs (against XBB.1.16, CH.1.1, or BA.4/BA.5) at pre-dose and 1 month post dose were higher for participants with evidence of prior SARS-CoV-2 infection at baseline (baseline positive) compared with those without evidence of prior SARS-CoV-2 infection at baseline (baseline negative).

Similar results were observed for participants with or without evidence of prior SARS-CoV-2 infection in the all-available immunogenicity population.

Participants Without Evidence of Infection

Among participants in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection up to 1 month after the study vaccination:

- The observed GMTs at 1-month post dose against Omicron variant XBB.1.16 and Omicron CH.1.1 were higher in the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg group compared to the BNT162b2 30-µg group.
- Despite different intervals from dose 3 to 4, the pre-dose 4 neutralizing titres against Omicron variant XBB.1.16 and CH.1.1 were similar for the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg and BNT162b2 30-µg vaccine groups.

Table 12. Geometric Mean Titres, by Baseline SARS-CoV-2 Status – XBB.1.16 and CH.1.1 Neutralization – Subset of Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Participants >55 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		C4591031 BNT162b2 30 µg	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron XBB.1.16 - NT50 (titer)	All	Prevax	36	18.7 (13.3, 26.3)	37	27.5 (18.0, 41.9)
		1 Month	36	93.3 (60.5, 144.0)	37	42.3 (27.6, 64.8)
	Positive[d]	Prevax	19	28.3 (16.1, 49.8)	17	63.9 (31.4, 130.0)
		1 Month	19	135.8 (75.0, 245.6)	17	100.1 (52.5, 190.9)
	Negative[e]	Prevax	17	11.8 (9.0, 15.4)	20	13.4 (10.7, 16.9)
		1 Month	17	61.4 (32.4, 116.2)	20	20.3 (14.4, 28.7)
SARS-CoV-2 FFRNT - Omicron CH.1.1 - NT50 (titer)	All	Prevax	36	15.0 (11.4, 19.6)	37	19.3 (13.9, 26.8)
		1 Month	36	59.4 (38.5, 91.4)	37	25.0 (17.3, 36.2)
	Positive[d]	Prevax	19	20.7 (12.9, 33.4)	17	35.4 (19.7, 63.7)
		1 Month	19	90.9 (48.5, 170.3)	17	53.2 (29.4, 96.2)
	Negative[e]	Prevax	17	10.4 (9.6, 11.4)	20	11.5 (9.7, 13.6)
		1 Month	17	36.9 (21.0, 64.7)	20	13.2 (10.3, 16.9)
SARS-CoV-2 FFRNT - Omicron BA.4/BA.5 - NT50 (titer)	All	Prevax	36	105.8 (60.2, 185.9)	37	124.2 (68.3, 225.9)
		1 Month	36	1196.6 (791.2, 1809.7)	37	278.1 (174.1, 444.1)
	Positive[d]	Prevax	19	338.0 (190.4, 600.1)	17	384.4 (162.8, 908.0)
		1 Month	19	2019.6 (1297.9, 3142.5)	17	784.7 (433.0, 1422.1)
	Negative[e]	Prevax	17	28.9 (16.9, 49.4)	20	47.6 (26.2, 86.4)
		1 Month	17	666.6 (345.5, 1286.4)	20	115.1 (75.2, 176.2)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Approximately forty participants (20 baseline SARS-CoV-2 positive status and 20 negative status) were selected from >55 years age group in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and from Study C4591031 Substudy E expanded cohort (>55 years) BNT162b2 30-µg group.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 17MAY2023 (22:08)
(Data cutoff date : C4591044 [15Nov2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C2_XBB116CMB/adva_s001_gmt_bs_xbb2_evl_c2

Assessor´s comment: The FFRNT assay is a non-validated nautralization assay. Geometric Mean Fold Rises and seroresponses for Omicron XBB.1.5, XBB.1.16 and CH.1.1 was shown by the applicant, but are not presented in this AR as the GMTs for these types were very low indicating no cross-neutralization for these types. The cross-neutralizing antibody level against XBB.1.5, XBB.1.16 and CH.1.1 were so low, that no clinically important protection against Covid-19 caused by these types is expected after the bivalent Original/Omi BA.4-5 vaccination.

T-Cell Responses in PBMC Subset (Cohort 2)

C4591044 Cohort 2 and Cohort 3 Combined: 6-Month Analysis Final CSR [dated 24 June 2024] presents the full details and outputs of the PBMC analyses summarised below.

CD4 and CD8 T-Cell Cytokine Response – Spike Pool 1

IFN γ *Positive Response – CD4+ and CD8+ T-Cells*

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, frequencies of CD4+ and CD8+ T-cells secreting IFN γ in response to spike pool 1 increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age, with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1.

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, frequencies of CD4+ and CD8+ T-cells secreting IFN γ in response to spike pool 1 increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age, with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1.

Across both dose and age groups, the frequencies of CD4+ and CD8+ T-cells secreting IFN γ in response to spike pool 1 peaked 1-week post vaccination and tapered off for the remaining timepoints. Both dose groups had similar GMFRs for IFN γ+ (% of CD4 and CD8).

CD4 and CD8 T-Cell Cytokine Response – Spike Pool 2

IFN γ *Positive Response – CD4+ and CD8+ T-Cells*

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, frequencies of CD4+ and CD8+ T-cells secreting IFN γ in response to spike pool 2 increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age, with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1.

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, frequencies of CD4+ and CD8+ T-cells secreting IFN γ in response to spike pool 2 increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age, with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1.

Across both dose and age groups, the frequencies of CD4+ and CD8+ T-cells secreting IFN γ in response to spike pool 2 peaked 1-week post vaccination and tapered off for the remaining timepoints. Both dose groups had similar GMFRs for IFNγ+ (% of CD4 and CD8).

CD4 and CD8 T-Cell Cytokine Response – Unique Wild Type Spike

IFN γ *Positive Response – CD4+ T-cells*

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, frequencies of CD4+ T-cells secreting IFN γ in response to unique wild type spike increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age (GMFR=1.4 and 1.6, respectively), with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1 (GMFR=1.1 and 1.4, 0.9 and 1.4, 1.1 and 1.0, respectively).

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, frequencies of CD4+ T-cells secreting IFN γ in response to unique wild type spike increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age (GMFR=2.3 and 1.8, respectively), with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1 (GMFR=1.3 and 1.5, 1.1 and 1.2, 1.2 and 0.9, respectively).

Across both dose and age groups, the frequencies of CD4+ T-cells secreting IFN γ in response to unique wild type spike peaked 1-week post vaccination and tapered off for the remaining timepoints. Both dose groups had similar GMFRs for IFN γ+ (% of CD4).

IFN γ Positive Response – CD8+ T-cells

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, frequencies of CD8+ T-cells secreting IFN γ in response to unique wild type spike increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age (GMFR=1.4 and 1.8, respectively), with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1 (GMFR=1.2 and 1.6, 1.3 and 1.5, 1.1 and 1.4, respectively).

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, frequencies of CD8+ T-cells secreting IFNγ in response to unique wild type spike increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age (GMFR=1.7 and 1.8, respectively), with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1 (GMFR=1.2 and 1.4, 1.2 and 1.3, 1.2 and 1.3, respectively).

Across both dose and age groups, the frequencies of CD8+ T-cells secreting IFN□ in response to unique Omicron BA.4/BA.5 spike peaked 1-week post vaccination and tapered off for the remaining timepoints. Both dose groups had similar GMFRs for IFNγ+ (% of CD8).

<u>CD4 and CD8 T-Cell Cytokine Response – Unique Omicron BA.4/BA.5 Spike</u>

IFN γ Positive Response – CD4+ T-cells

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, frequencies of CD4+ T-cells secreting IFN γ in response to unique Omicron BA.4/BA.5 spike increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age (GMFR=1.4 and 1.5, respectively), with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1 (GMFR=1.0 and 1.4, 0.9 and 1.3, 1.0 and 1.0, respectively).

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, frequencies of CD4+ T-cells secreting IFN γ in response to unique Omicron BA.4/BA.5 spike increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age (GMFR=1.8 and 2.1, respectively), with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1 (GMFR=1.1 and 1.4, 1.0 and 1.1, 1.0 and 0.9, respectively).

Across both dose and age groups, the frequencies of CD4+ T-cells secreting IFN□ in response to unique Omicron BA.4/BA.5 spike peaked 1-week post vaccination and tapered off for the remaining timepoints. Both dose groups had similar GMFRs for IFNγ+ (% of CD4).

IFN γ Positive Response – CD8+ T-cells

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, frequencies of CD8+ T-cells secreting IFN γ in response to unique Omicron BA.4/BA.5 spike increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age (GMFR=1.4 and 1.6, respectively), with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1 (GMFR=1.2 and 1.5, 1.2 and 1.4, 1.2 and 1.3, respectively).

In the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, frequencies of CD8+ T-cells secreting IFN γ in response to unique Omicron BA.4/BA.5 spike increased from before vaccination to 1 week after study vaccination in participants 18 through 55 years of age and >55 years of age (GMFR=1.6 and 1.5, respectively), with lower responses at 1, 3, and 6 months after study vaccination compared with Week 1 (GMFR=1.3 and 1.3, 1.2 and 1.2, 1.2 and 1.2, respectively).

Across both dose and age groups, the frequencies of CD8+ T-cells secreting IFN γ in response to unique Omicron BA.4/BA.5 spike peaked 1-week post vaccination and tapered off for the remaining timepoints. Both dose groups had similar GMFRs for IFNγ+ (% of CD8).

HLA Type

All participants >18 years of age in Cohort 2 who consented to PBMC isolation and HLA typing were included in the Cohort 2 PBMC subset population.

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, the evaluable immunogenicity population consisted of 20 participants 18 through 55 years of age and 20 participants >55 years of age. The majority of participants 18 through 55 and >55 years of age (75.0% and 90.0%, respectively) had an HLA allele of DPA1*01:03:01G.

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, the evaluable immunogenicity population consisted of 28 participants 18 through 55 years of age and 16 participants >55 years of age. The majority of participants 18 through 55 (89.3%) and all participants >55 years of age had an HLA allele of DPA1*01:03:01G.

Immunogenicity Conclusions

Persistence of Immune Response: BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30 µg

Analysis of immunogenicity data at 6 months after vaccination in a subset of BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age with or without evidence of prior SARS-CoV-2 infection from Cohort 2 and Cohort 3 combined who received a booster (Dose 4) of BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30 µg demonstrated a persistent vaccine-elicited immune response through 6 months after study vaccination.

- Increased neutralizing responses with BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) were observed regardless of baseline SARS-CoV-2 infection status, with the greatest GMFRs observed in participants without prior infection and the higher neutralizing titres observed in participants with prior infection.
- Across all age groups within baseline positive and baseline negative groups, Omicron BA.4/BA.5 neutralizing GMTs were observed to be highest at 1 month after study vaccination and gradually decreased at 3 and 6 months after study vaccination. However, at the 6-month timepoint, GMTs were still considerably higher than the baseline value across all age groups.
- Within baseline negative groups at the 6-month timepoint, reference strain neutralizing GMTs were still considerably higher than the baseline value across all age groups.
- Omicron BA.4/BA.5 and reference strain GMFRs were highest at 1 month and gradually decreased at 3 and 6 months after study vaccination. Omicron BA.4/BA.5 GMFRs remained

high up to 6 months after study vaccination across all age groups within baseline negative and baseline positive groups. Reference strain GMFRs remained high up to 6 months after study vaccination across all age groups within baseline negative groups.

- Seroresponse rates to Omicron BA.4/BA.5 remained high at 6 months after study vaccination across all age groups within baseline negative and baseline positive groups. Seroresponse rates to the reference strain remained high at 6 months after study vaccination across all age groups within baseline negative groups. Seroresponse rates to the reference strain were lowest at 6 months after study vaccination across all age groups within baseline positive groups.

Neutralization of Variants: BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg

The cross-neutralization antibody levels against Omicron XBB.1.5, XBB.1.16, and CH.1.1 were very low after ORIGINAL/OMI BA.4-.5 vaccination.

T-Cell Responses (Cohort 2)

Frequencies of CD4+ T-cells secreting 2 of 3 Th1 cytokines (IL-2, TNF α, IFN γ) in response to S1, S2, unique Omicron WT and unique Omicron BA.4/BA.5 pools generally peaked at 1 week post vaccination increased slightly post-Dose 1 and remained unchanged at all other timepoints. This trend was observed across both age groups and dose levels. IFN γ CD107a producing CD8 T-cells also produced a similar pattern. Finally, there was a skewing of the CD4 T-cell population towards IFN γ production rather than IL-4, suggesting a Th1-biased response. Th1 cells are responsible for mediating a cellular immune response to virally infected cells, such as SARS-CoV-2.

On comparison of the 2 doses utilized in this study (BNT162b2 Bivalent [ORIGINAL/OMI BA.4-.5] 30 µg or 60 µg), both doses consistently yielded similar GMFRs for CD4+ and CD8+ T-cells secreting IFN γ Additionally, across both doses and age groups, the magnitude of CD4+ and CD8+ T-cell response to spike pool 1 was higher than that to spike pool 2.

7.3. Discussion

In the current application, immunogenicity data from **study C4591044**, where the BNT162b2 Bivalent (WT/OMI BA.4-5) was given as the fourth dose (second booster) in participant ≥12 years of age. The 1 month post booster data was evaluated earlier. The aims of the currently presented exploratory immunogenicity analysis were to follow up the antibody persistance over 3 and 6 months post vaccination, to explore cross- neutralizing antibodies to other newly circulating omicron variants and describe the cell- mediated immunity after the vaccination with bivalent original/Omicron BA.4-5 vaccine. The analysis were descriptive, which was agreed to earlier. The methodology of this study has been assessed during earlier procedures, found to be acceptable and therefore it is not repeated here again.

Persistent antibody levels were observed up to 6 months post vaccination in all age groups regardless of baseline Covid-19 experience status. The adolescent group demonstrated higher neutralizing antibody levels than adults and older adults as expected. All participants had high a level of neutralizing antibodies against Wt strain at the baseline due to the recent vaccination (less than 1 year ago) with Original vaccine. GMTs were observed to be highest at 1 month after study vaccination and gradually decreased at 3 and 6 months after study vaccination. However, at the 6-month timepoint, GMTs were still considerably higher than the baseline value across all age groups. The seroresponse rate, defined as percentage of participants achieving a ≥4-fold rise from baseline (before the study vaccination) at each timepoint after vaccination (or postvaccination assay result ≥4 × LLOQ if the baseline measurement was below LLOQ), depends of the baseline antibody level. If the baseline antibody level is already high, it is not biologically

possible to reach 4 fold rise after the vaccination. Therefore, seroresponse rate is not very informative in case of booster vaccination.

The non-validated FFRNT assay was used to evaluate cross-neutralizing responses to Omicron XBB.1.5, XBB.1.16 and CH.1.1. The GMTs for these types were very low indicating no cross-neutralization for these types. No clinically important protection against Covid-19 caused by these types is expected after the bivalent Original/Omi BA.4-5 vaccination.

T-cell responses generally peaked at 1 week post vaccination increased slightly post-Dose 1 and remained unchanged at all other timepoints. This trend was observed across both age groups and dose levels.

There was a skewing of the CD4 T-cell population towards IFN-γ production rather than IL-4, suggesting a Th1-biased response. This is an expected result as Th1 cells are responsible for mediating a cellular immune response to virally infected cells, such as SARS-CoV-2.

In conclusion, the bivalent Original/Omi BA4-5 induced sustainable level of neutralizing antibodies specific to Omi BA4-5 and Wt up to 6 months post booster. The highest T- cell responses peaked 1 week post booster and indicated Th1-biased response. The cross-neutralizing antibodies to other relevant Omicron variants were very low and no protection against these is expected after the WT/OMI BA4-5 booster.

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

8.1.1. Study C4591044

This report includes AEs and SAEs reported from study vaccination through 6 months vaccination. Methods and safety data for participants who received a 30 or 60-µg dose of BNT162b2 Original/BA.4-5) as Dose 4, including local reactions and systemic events recorded in the e-diary for 7 days after vaccination through 1 month after study vaccination were previously described in EMEA/H/C/005735/II/0177/G.

8.2. Results

8.2.1. Study C4591044

An overview of AEs reported from study vaccination through 6 months after study vaccination is shown below.

Table 13. Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through 6 Months After the Study Vaccination –Cohort 2 and Cohort 3 Combined – Safety Population

	Vaccine Group (as Administered)				
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)				
	12-17 Years	18-55 Years		>55 Years	
	30 µg (N[a]=107)	30 µg (N[a]=313)	60 µg (N[a]=110)	30 µg (N[a]=306)	60 µg (N[a]=102)
Adverse Event	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any adverse event	11 (10.3)	26 (8.3)	12 (10.9)	33 (10.8)	14 (13.7)
Related[c]	5 (4.7)	13 (4.2)	3 (2.7)	6 (2.0)	2 (2.0)
Severe	1 (0.9)	3 (1.0)	1 (0.9)	9 (2.9)	0
Life-threatening	0	0	0	1 (0.3)	0
Any serious adverse event	1 (0.9)	2 (0.6)	1 (0.9)	10 (3.3)	0
Related[c]	0	0	0	0	0
Severe	1 (0.9)	2 (0.6)	1 (0.9)	8 (2.6)	0
Life-threatening	0	0	0	1 (0.3)	0
Any nonserious adverse event	10 (9.3)	25 (8.0)	12 (10.9)	26 (8.5)	14 (13.7)
Related[c]	5 (4.7)	13 (4.2)	3 (2.7)	6 (2.0)	2 (2.0)
Severe	0	1 (0.3)	0	2 (0.7)	0
Life-threatening	0	0	0	0	0
Any adverse event leading to withdrawal	1 (0.9)	0	0	1 (0.3)	0
Related[c]	0	0	0	0	0
Severe	0	0	0	0	0
Life-threatening	0	0	0	1 (0.3)	0
Death	0	0	0	1 (0.3)	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 the study intervention.
PFIZER CONFIDENTIAL SDTM Creation: 25SEP2023 (09:47) Source Data: adaexa Table Generation: 27SEP2023 (14:18)
(Database snapshot date: 21SEP2023) Output File: ./nda2_ub1044/C4591044_C23_6MPD/adae_091_6m_c23

Many of the AEs were consistent with reactogenicity events (eg, fatigue, injection site pain or erythema, chills, headache), and included lymphadenopathy.

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, 11 participants (10.3%) 12 through 17 years of age, 26 participants (8.3%) 18 through 55 years of age, and 33 participants (10.8%) >55 years of age, reported any AE:

- Of the 11 participants 12 through 17 years of age who reported an AE, the SOC containing the most frequently reported AEs was general disorders and administration site conditions (3.7%). All other SOCs were reported by 1.9% of participants or less.
- Of the 26 participants 18 through 55 years of age who reported an AE, the SOC containing the most frequently reported AEs was blood and lymphatic system disorders (2.6%) followed by infections and infestations (1.6%) and general disorders and
- administration site conditions (1.3%). The most commonly reported PT in the blood and lymphatic system disorders SOC was lymphadenopathy and was reported by 6 participants (1.9%).
- Of the 33 participants >55 years of age who reported an AE, the SOC containing the most frequently reported AEs was musculoskeletal and connective tissue orders (2.6%), followed by infections and infestations (2.0%). One participant reported an AE of elevated troponin 22 days after study vaccination and was evaluated for potential myocarditis/pericarditis. Troponin T and ECG results were both abnormal and echo was normal. The AE was not considered to be myocarditis/pericarditis and was assessed as not related to study vaccination by the investigator.

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, 12 participants (10.9%) 18 through 55 years of age and 14 participants (13.7%) >55 years of age reported any AE:

- Of the 12 participants 18 through 55 years of age who reported an AE, the SOC containing the most frequently reported AEs was infections and infestations (2.7%), blood and lymphatic system disorders (1.8%), and reproductive system and breast disorders (1.8%).
- Of the 14 participants >55 years of age who reported an AE, the SOC containing the most frequently reported AEs was injury, poisoning and procedural complications and musculoskeletal and connective tissue disorders (2.9% each) followed by infections and infestations (2.0%). One participant reported an AE of dyspnea 20 days after study vaccination that lasted for 2 days and was evaluated for potential myocarditis/pericarditis. Troponin T and ECG results were both normal. The AE was not considered to be myocarditis/pericarditis and was assessed as not related to study vaccination by the investigator.

Table 14. Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through 6 Months After the Study Vaccination, by System Organ Class and Preferred Term – Cohort 2 and Cohort 3 Combined – Safety Population

	Vaccine Group (as Administered)									
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)									
	12-17 Years		18-55 Years				>55 Years			
	30 µg (N[a]=107)		30 µg (N[a]=313)		60 µg (N[a]=110)		30 µg (N[a]=306)		60 µg (N[a]=102)	
System Organ Class Preferred Term	n[b] (%)	(95% CI [c])	n[b] (%)	(95% CI [c])	n[b] (%)	(95% CI [c])	n[b] (%)	(95% CI [c])	n[b] (%)	(95% CI [c])
Any adverse event	11 (10.3)	(5.2, 17.7)	26 (8.3)	(5.5, 11.9)	12 (10.9)	(5.8, 18.3)	33 (10.8)	(7.5, 14.8)	14 (13.7)	(7.7, 22.0)
Blood and lymphatic system disorders	0	(0.0, 3.4)	8 (2.6)	(1.1, 5.0)	2 (1.8)	(0.2, 6.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Lymphadenopathy	0	(0.0, 3.4)	6 (1.9)	(0.7, 4.1)	1 (0.9)	(0.0, 5.0)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Anaemia	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Iron deficiency anaemia	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Lymphadenitis	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Cardiac disorders	1 (0.9)	(0.0, 5.1)	0	(0.0, 1.2)	0	(0.0, 3.3)	3 (1.0)	(0.2, 2.8)	1 (1.0)	(0.0, 5.3)
Arrhythmia	1 (0.9)	(0.0, 5.1)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Atrial fibrillation	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Left ventricular failure	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Supraventricular extrasystoles	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Endocrine disorders	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Hypogonadism	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Eye disorders	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Corneal degeneration	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Gastrointestinal disorders	0	(0.0, 3.4)	3 (1.0)	(0.2, 2.8)	1 (0.9)	(0.0, 5.0)	3 (1.0)	(0.2, 2.8)	0	(0.0, 3.6)
Anal incontinence	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Constipation	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Diarrhoea	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Frequent bowel movements	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Hiatus hernia	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Inguinal hernia	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Irritable bowel syndrome	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Mouth swelling	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)

Oesophagitis	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
General disorders and administration site conditions	4 (3.7)	(1.0, 9.3)	4 (1.3)	(0.3, 3.2)	1 (0.9)	(0.0, 5.0)	2 (0.7)	(0.1, 2.3)	1 (1.0)	(0.0, 5.3)
Fatigue	3 (2.8)	(0.6, 8.0)	2 (0.6)	(0.1, 2.3)	1 (0.9)	(0.0, 5.0)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Injection site pain	2 (1.9)	(0.2, 6.6)	2 (0.6)	(0.1, 2.3)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	1 (1.0)	(0.0, 5.3)
Chills	1 (0.9)	(0.0, 5.1)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Injection site erythema	1 (0.9)	(0.0, 5.1)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Injection site swelling	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Pyrexia	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Hepatobiliary disorders	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Cholecystitis	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Infections and infestations	2 (1.9)	(0.2, 6.6)	5 (1.6)	(0.5, 3.7)	3 (2.7)	(0.6, 7.8)	6 (2.0)	(0.7, 4.2)	2 (2.0)	(0.2, 6.9)
Sinusitis	2 (1.9)	(0.2, 6.6)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Diverticulitis	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Localised infection	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Urinary tract infection	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Acute sinusitis	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Breast cellulitis	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Epstein-Barr virus infection	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Helicobacter infection	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Herpes zoster	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Oral herpes	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Otitis externa	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Post procedural infection	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Tooth abscess	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Injury, poisoning and procedural complications	2 (1.9)	(0.2, 6.6)	1 (0.3)	(0.0, 1.8)	1 (0.9)	(0.0, 5.0)	4 (1.3)	(0.4, 3.3)	3 (2.9)	(0.6, 8.4)
Fall	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	3 (1.0)	(0.2, 2.8)	1 (1.0)	(0.0, 5.3)
Contusion	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Skin laceration	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	1 (1.0)	(0.0, 5.3)
Alcohol poisoning	1 (0.9)	(0.0, 5.1)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Back injury	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Forearm fracture	1 (0.9)	(0.0, 5.1)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Head injury	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Ligament rupture	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Limb injury	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Muscle rupture	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Road traffic accident	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Tibia fracture	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Investigations	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	2 (0.7)	(0.1, 2.3)	0	(0.0, 3.6)
Intraocular pressure increased	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Troponin increased	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Metabolism and nutrition disorders	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	1 (0.9)	(0.0, 5.0)	3 (1.0)	(0.2, 2.8)	0	(0.0, 3.6)
Hypercholesterolaemia	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Hypoglycaemia	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Hypokalaemia	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Type 2 diabetes mellitus	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Vitamin D deficiency	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Musculoskeletal and connective tissue disorders	2 (1.9)	(0.2, 6.6)	1 (0.3)	(0.0, 1.8)	1 (0.9)	(0.0, 5.0)	8 (2.6)	(1.1, 5.1)	3 (2.9)	(0.6, 8.4)
Back pain	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	2 (0.7)	(0.1, 2.3)	1 (1.0)	(0.0, 5.3)

Arthralgia	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	1 (1.0)	(0.0, 5.3)
Myalgia	2 (1.9)	(0.2, 6.6)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Exostosis	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Joint range of motion decreased	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Muscle spasms	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Musculoskeletal pain	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Pain in extremity	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Sacral pain	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Tendonitis	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	1 (0.9)	(0.0, 5.0)	3 (1.0)	(0.2, 2.8)	0	(0.0, 3.6)
Adenocarcinoma pancreas	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Leukaemia	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Lipoma	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Prostate cancer	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Testicular germ cell cancer	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Nervous system disorders	1 (0.9)	(0.0, 5.1)	2 (0.6)	(0.1, 2.3)	1 (0.9)	(0.0, 5.0)	4 (1.3)	(0.4, 3.3)	0	(0.0, 3.6)
Headache	1 (0.9)	(0.0, 5.1)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Dizziness	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Focal dyscognitive seizures	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Presyncope	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Sciatica	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Syncope	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Psychiatric disorders	2 (1.9)	(0.2, 6.6)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	3 (1.0)	(0.2, 2.8)	1 (1.0)	(0.0, 5.3)
Depression	1 (0.9)	(0.0, 5.1)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	1 (1.0)	(0.0, 5.3)
Anxiety	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	2 (0.7)	(0.1, 2.3)	0	(0.0, 3.6)
Suicidal ideation	1 (0.9)	(0.0, 5.1)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Renal and urinary disorders	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	1 (0.9)	(0.0, 5.0)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Nephrolithiasis	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Ureterolithiasis	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Urinary tract obstruction	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Reproductive system and breast disorders	0	(0.0, 3.4)	2 (0.6)	(0.1, 2.3)	2 (1.8)	(0.2, 6.4)	0	(0.0, 1.2)	0	(0.0, 3.6)
Intermenstrual bleeding	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Menstruation irregular	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Scrotal mass	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Vaginal prolapse	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Respiratory, thoracic and mediastinal disorders	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	1 (1.0)	(0.0, 5.3)
Cough	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Dyspnoea	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Rales	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Skin and subcutaneous tissue disorders	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	3 (1.0)	(0.2, 2.8)	1 (1.0)	(0.0, 5.3)
Blood blister	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Erythema	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Pruritus	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Psoriasis	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Rash	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Urticaria	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Vascular disorders	0	(0.0, 3.4)	2 (0.6)	(0.1, 2.3)	0	(0.0, 3.3)	2 (0.7)	(0.1, 2.3)	1 (1.0)	(0.0, 5.3)
Hypertension	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Arteriosclerosis	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Hypotension	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Lymphoedema	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)

Note: MedDRA (v26.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 25SEP2023 (09:47) Source Data: adaexa Table Generation: 27SEP2023 (09:08)
(Database snapshot date: 21SEP2023) Output File: ./nda2_ub1044/C4591044_C23_6MPD/adae_130_6m_c23

Related Adverse Events

Table 15. Number (%) of Participants Reporting at Least 1 Related Adverse Event From the Study Vaccination Through 6 Months After the Study Vaccination, by System Organ Class and Preferred Term – Cohort 2 and Cohort 3 Combined – Safety Population

	Vaccine Group (as Administered)									
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)									
	12-17 Years		18-55 Years				>55 Years			
	30 µg (N[a]=107)		30 µg (N[a]=313)		60 µg (N[a]=110)		30 µg (N[a]=306)		60 µg (N[a]=102)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	5 (4.7)	(1.5, 10.6)	13 (4.2)	(2.2, 7.0)	3 (2.7)	(0.6, 7.8)	6 (2.0)	(0.7, 4.2)	2 (2.0)	(0.2, 6.9)
Blood and lymphatic system disorders	0	(0.0, 3.4)	7 (2.2)	(0.9, 4.6)	1 (0.9)	(0.0, 5.0)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Lymphadenopathy	0	(0.0, 3.4)	6 (1.9)	(0.7, 4.1)	1 (0.9)	(0.0, 5.0)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Lymphadenitis	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Gastrointestinal disorders	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Diarrhoea	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Frequent bowel movements	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
General disorders and administration site conditions	4 (3.7)	(1.0, 9.3)	4 (1.3)	(0.3, 3.2)	1 (0.9)	(0.0, 5.0)	2 (0.7)	(0.1, 2.3)	1 (1.0)	(0.0, 5.3)
Fatigue	3 (2.8)	(0.6, 8.0)	2 (0.6)	(0.1, 2.3)	1 (0.9)	(0.0, 5.0)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Injection site pain	2 (1.9)	(0.2, 6.6)	2 (0.6)	(0.1, 2.3)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	1 (1.0)	(0.0, 5.3)
Chills	1 (0.9)	(0.0, 5.1)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Injection site erythema	1 (0.9)	(0.0, 5.1)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Injection site swelling	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Pyrexia	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Infections and infestations	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Oral herpes	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Musculoskeletal and connective tissue disorders	2 (1.9)	(0.2, 6.6)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Myalgia	2 (1.9)	(0.2, 6.6)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Nervous system disorders	1 (0.9)	(0.0, 5.1)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Headache	1 (0.9)	(0.0, 5.1)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Reproductive system and breast disorders	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Menstruation irregular	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Respiratory, thoracic and mediastinal disorders	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Cough	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Skin and subcutaneous tissue disorders	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	2 (0.7)	(0.1, 2.3)	1 (1.0)	(0.0, 5.3)
Erythema	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Pruritus	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Psoriasis	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	1 (1.0)	(0.0, 5.3)
Urticaria	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Vascular disorders	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Lymphoedema	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)

Note: MedDRA (v26.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 25SEP2023 (09:47) Source Data: adaexa Table Generation: 27SEP2023 (09:08)
(Database snapshot date: 21SEP2023) Output File: ./nda2_ub1044/C4591044_C23_6MPD/adae_130_rel_6m_c23

Severe or Life-Threatening Adverse Events

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, 1 participant (0.9%) 12 through 17 years of age, 3 participants (1.0%) 18 through 55 years of age, and 10 participants (3.3%) >55 years of age, reported a severe or life-threatening AE.

- The participant 12 through 17 years of age reported severe AEs of alcohol poisoning and suicidal ideation. These severe events were also SAEs. No life-threatening AEs were reported.
- Of the 3 participants 18 through 55 years of age who reported a severe or life-threatening AE, 1 participant (0.3%) each reported severe AEs of diverticulitis, hypertension, and hypotension. The 2 severe events of diverticulitis and hypotension were also SAEs. No life-threatening AEs were reported.
- Of the 10 participants >55 years of age who reported a severe or life-threatening AE, all PTs were reported by 1 participant (0.3%) each. The most commonly reported SOCs were metabolism and nutrition disorders and neoplasms benign, malignant and unspecified (incl cysts and polyps), with each reported by 3 participants (1.0%). All severe AEs were classified as SAEs (except for fall, head injury, ligament rupture, and muscle rupture). One participant (0.3%) reported a life-threatening AE of left ventricular failure (see section death).

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, 1 participant (0.9%) 18 through 55 years of age reported a severe SAE of testicular germ cell cancer. No participants >55 years of age reported a severe or life-threatening AE.

Deaths

One death was reported from the study vaccination through 6 months after study vaccination. This participant was 71 years of age with a history of hypertension and hypercholesterolemia. On D69 after vaccination (WT/OMI BA.4-5 at 30 µg) the participant underwent surgery for removal of benign bladder tumour and during the surgery a left ventricular failure was developed, and a stent placement was executed. About 3 weeks after the surgery the participant died due to cardiac failure. In the opinion of the investigator and sponsor, there was no reasonable possibility that the left ventricular failure was related to the study intervention.

Serious Adverse Events

Cohort 2

For the Cohort 2 BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, 4 participants (3.8%) >55 years of age, reported SAEs of arrhythmia, adenocarcinoma pancreas, leukemia, prostate cancer, and syncope. No participants 18 through 55 years of age reported an SAE. All SAEs except syncope were severe.

Cohort 2 and Cohort 3 Combined

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, 1 participant (0.9%) 12 through 17 years of age, 2 participants (0.6%) 18 through 55 years of age, and 10 participants (3.3%) >55 years of age, reported SAEs:

- The participant 12 through 17 years of age reported severe SAEs of alcohol poisoning and suicidal ideation.

- Of the 2 participants 18 through 55 years of age who reported SAEs, 1 participant (0.3%) each reported severe SAEs of diverticulitis and hypotension.
- Of the 10 participants >55 years of age who reported SAEs, 1 participant (0.3%) each reported severe SAEs of arrhythmia, left ventricular failure, post procedural infection, hypoglycemia, hypokalemia, Type 2 diabetes mellitus, adenocarcinoma pancreas, leukemia, prostate cancer, and urinary tract obstruction.

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, 1 participant (0.9%) 18 through 55 years of age experienced a severe SAE of testicular germ cell cancer. No participants >55 years of age reported an SAE.

Table 16. Number (%) of Participants Reporting at Least 1 Serious Adverse Event From the Study Vaccination Through 6 Months After the Study Vaccination, by System Organ Class and Preferred Term – Cohort 2 and Cohort 3 Combined – Safety Population

	Vaccine Group (as Administered)									
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)									
	12-17 Years		18-55 Years				>55 Years			
	30 µg (N[a]=107)		30 µg (N[a]=313)		60 µg (N[a]=110)		30 µg (N[a]=306)		60 µg (N[a]=102)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	1 (0.9)	(0.0, 5.1)	2 (0.6)	(0.1, 2.3)	1 (0.9)	(0.0, 5.0)	10 (3.3)	(1.6, 5.9)	0	(0.0, 3.6)
Cardiac disorders	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	2 (0.7)	(0.1, 2.3)	0	(0.0, 3.6)
Arrhythmia	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Left ventricular failure	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Infections and infestations	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Diverticulitis	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Post procedural infection	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Injury, poisoning and procedural complications	1 (0.9)	(0.0, 5.1)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Alcohol poisoning	1 (0.9)	(0.0, 5.1)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Metabolism and nutrition disorders	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	3 (1.0)	(0.2, 2.8)	0	(0.0, 3.6)
Hypoglycaemia	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Hypokalaemia	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Type 2 diabetes mellitus	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Musculoskeletal and connective tissue disorders	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Back pain	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	3 (1.0)	(0.2, 2.8)	0	(0.0, 3.6)

Adenocarcinoma pancreas	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Leukaemia	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Prostate cancer	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Testicular germ cell cancer	0	(0.0, 3.4)	0	(0.0, 1.2)	1 (0.9)	(0.0, 5.0)	0	(0.0, 1.2)	0	(0.0, 3.6)
Nervous system disorders	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Syncope	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Psychiatric disorders	1 (0.9)	(0.0, 5.1)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Suicidal ideation	1 (0.9)	(0.0, 5.1)	0	(0.0, 1.2)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Renal and urinary disorders	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Urinary tract obstruction	0	(0.0, 3.4)	0	(0.0, 1.2)	0	(0.0, 3.3)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.6)
Vascular disorders	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)
Hypotension	0	(0.0, 3.4)	1 (0.3)	(0.0, 1.8)	0	(0.0, 3.3)	0	(0.0, 1.2)	0	(0.0, 3.6)

Note: MedDRA (v26.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 25SEP2023 (09:47) Source Data: adaexa Table Generation: 27SEP2023 (09:14)
(Database snapshot date: 21SEP2023) Output File: ./nda2_ub1044/C4591044_C23_6MPD/adae_130_ser_6m_c23

Discontinuations Due to Adverse Events

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, 1 participant (0.9%) 12 through 17 years of age withdrew because of depression and 1 participant (0.3%) >55 years of age withdrew because of left ventricular failure, which led to death. Neither of the AEs were assessed as related to study vaccination by the investigator.

Adverse Events of Special Interest

No cases of myocarditis and/or pericarditis were reported up to 6 months after study vaccination.

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, 1 participant (0.9%) 12 through 17 years of age, 5 participants (1.6%) 18 through 55 years of age, and 9 participants (2.9%) >55 years of age, reported AESIs.

- The participant 12 through 17 years of age reported an AESI of arrhythmia.
- Of the 5 participants 18 through 55 years of age who reported AESIs, 1 participant (0.3%) each reported AESIs of oral herpes, intermenstrual bleeding, cough, urticaria, and hypotension.
- Of the 9 participants >55 years of age who reported AESIs, 1 participant (0.3%) each reported AESIs of arrhythmia, mouth swelling, pyrexia, herpes zoster, contusion, arthralgia, focal dyscognitive seizures, blood blister, erythema, and pruritus.

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, 1 participant (0.9%) 18 through 55 years of age reported an AESI of contusion and 3 participants (2.9%) >55 years of age reported any AESI. One participant each (1.0%) reported AESIs of arthralgia, dyspnea, psoriasis, and rash.

Surveillance of COVID-19 Occurrences

Confirmed COVID-19 Occurrences

Overall, a total of 68 participants reported first COVID-19 occurrence. No participants reported a severe COVID-19 occurrence or MIS-C.

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, 4 participants (3.7%) 12 through 17 years of age, 28 participants (8.9%) 18 through 55 years of age, and 19 participants (6.2%) >55 years of age, reported first occurrence of COVID-19 after study vaccination:

- In participants 12 through 17 years of age, there were 2 participants (1.9%) who reported occurrences 31-60 days after study vaccination and 1 participant (0.9%) each reported the occurrence 121-150 days and 151-180 days after study vaccination. The most commonly reported symptom was rhinorrhea and was reported by all 4 participants (100.0%).
- In participants 18 through 55 years of age, the most frequently reported time frame for first COVID-19 occurrence was 61-90 days, 121-150 days, and 151-180 days after study vaccination, which were reported by 6 participants (1.9%) each. The most commonly reported symptoms were new or increased cough (22 participants [78.6%]), sore throat (19 participants [67.9%]), and rhinorrhea and new or increased nasal congestion, which were reported by 13 participants (46.4%) each.
- In participants >55 years of age, the most frequently reported time frame for first COVID-19 occurrence was 121-150 days after study vaccination and was reported by 5 participants (1.6%). The most commonly reported symptom was new or increased cough (16 participants [84.2%]), followed by new or increased nasal congestion, which was reported by 9 participants (47.4%).

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, 12 participants (10.9%) 18 through 55 years of age and 5 participants (4.9%) >55 years of age reported first occurrence of COVID-19 after study vaccination:

- In participants 18 through 55 years of age, the most frequently reported time frame for first COVID-19 occurrence was 1-30 days and 61-90 days after study vaccination and was reported by 3 participants (2.7%) each. The most commonly reported symptoms were new or increased cough (11 participants [91.7%]), sore throat (10 participants [83.3%]), and new or increased nasal congestion, which was reported by 8 participants (66.7%).
- In participants >55 years of age, the most frequently reported time frame for first COVID-19 occurrence was 91-120 days after study vaccination and was reported by 3 participants (2.9%). The most commonly reported symptoms were new or increased cough, new or increased muscle pain, and sore throat, which were reported by 4 participants (80.0%) each.

Variants of Concern for the First COVID-19 Occurrence

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 30-µg groups, 4 participants (3.7%) 12 through 17 years of age, 28 participants (8.9%) 18 through 55 years of age, and 19 participants (6.2%) >55 years of age, reported first occurrence of COVID-19 after study vaccination. Variants of concern for the first COVID-19 occurrence are summarised below:

- Among the determinate and quantifiable sequence results for COVID-19 occurrences reported in participants 12 through 17 years of age (n=4), lineage for the cases were identified as BA.4.6 (Omicron) (n= 1 [25.0%]), BF.7 (Omicron) (n= 1 [25.0%]), BQ.1.1.41 (Omicron) (n=1 [25.0%]), and XBB.1.5 (Omicron) (n= 1 [25.0%]).
- Among the determinate and quantifiable sequence results for COVID-19 cases reported in participants 18 through 55 years of age (n=28), the most frequently determined lineage was identified as XBB.1.5 (Omicron) (n= 4 [14.3%]) and 3 cases (10.7%) were unknown, which also included indeterminate results and nonquantifiable or not sequenced samples. Other Omicron variants were reported by 2 participants (7.1%) or less.

- Among the determinate and quantifiable sequence results for COVID-19 cases reported in participants >55 years of age (n=19), the most frequently determined lineage was identified as XBB.1.5 (Omicron) (n= 3 [15.8%]). Other Omicron variants were reported by 2 participants (10.5%) or less and 1 case (5.3%) was unknown, which also included indeterminate results and nonquantifiable or not sequenced samples.

For the BNT162b2 Bivalent (ORIGINAL/OMI BA.4-.5) 60-µg groups, 12 participants (10.9%) 18 through 55 years of age and 5 participants (4.9%) >55 years of age reported first occurrence of COVID-19 after study vaccination. Variants of concern for the first COVID-19 occurrence are summarised in below:

- Among the determinate and quantifiable sequence results for COVID-19 cases reported in participants 18 through 55 years of age (n=12), all Omicron lineages were reported by 1 participant (8.3%) each.
- Among the determinate and quantifiable sequence results for COVID-19 cases reported in participants >55 years of age (n=5), the most frequently determined lineage was identified as BQ.1.1 (Omicron) (n= 2 [40.0%]). Other Omicron variants (XBB.1.5, BQ.1, and BA.5.9) were reported by 1 participant (20%) each.

8.3. Discussion

This report includes AEs and SAEs reported from study vaccination through 6 months vaccination. Methods and safety data for participants who received a 30 or 60-µg dose of BNT162b2 Original/BA.4-5) as Dose 4, including local reactions and systemic events recorded in the e-diary for 7 days after vaccination through 1 month after study vaccination were previously described in EMEA/H/C/005735/II/0177/G.

During the reporting interval, any AEs were reported in 10-14% of the participants. Among these events, 2-5% were considered related to study vaccination. The participants aged >55 years reported the lowest frequency of related AEs (2%). Most of the related AEs were consistent with reactogenicity and PTs already included in the SmPC.

In total reported 13 participants SAEs. One participant in the age group reported alcohol poisoning, among the subjects aged 18-<55 years one participant reported diverticulitis and another hypotension. Nine participants aged >55 years reported SAEs which included arrhythmia, post procedural infection, hypoglycemia, hypokalemia, Type 2 diabetes mellitus, adenocarcinoma pancreas, leukemia, prostate cancer, and urinary tract obstruction. One participant aged >55 years died due to left ventricular failure. None of these events were considered related to study vaccination.

No cases of myocarditis and/or pericarditis were reported up to 6 months after study vaccination.

No new safety concern was identified.

A total of 68 participants reported covid-19 occurrence. Overall, the most frequently determined lineage was identified as XBB.1.5 (Omicron) which reflects the epidemiological situation of covid-19 at that time.

9. Risk management plan

On 24 September 2024 the MAH submitted an updated RMP version 13.1 (dated 22 September 2024) with this application.

Following liaising with EMA and PRAC Rapporteur, the MAH submitted on 15 November 2024 an updated RMP version 13.2 (dated 08 November 2024) alongside a corresponding justification document

addressing a request for a 9 month extension for the final CSR for study C4591021 (see below).

The MAH provided the following rationale for submitting an updated RMP:

- To remove the following completed studies/milestones from Part III.2, Part V and Annexes as applicable, for which the final CSRs have been submitted to EMA: C4591007, C4591015, C4591024, C4591031 SSE, C4591044, C4591014, and WI255886.
- To remove milestone of study C4591051 due to study termination as per PRAC's PAM-MEA-064.3 outcome.
- New milestone, key objectives, design and study population of interventional study C4591048 (a master phase 1/2/3 protocol to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b2 RNA-based vaccine candidate(s) in healthy children) were aligned according to Protocol Amendment (PA)#5.
- C4591038 final CSR milestone change from 30 September 2024 to 30 June 2025 as per ongoing PAM-MEA-047.5 procedure.
- New milestone for CSR submission of study C4591021 was updated due to the need to collect all necessary data and conduct analyses and quality control checks for the final study report. Whereas all data were extracted, and variables created, the end of data collection requires further time to be completed for the reasons outlined in the corresponding justification document.
- Other minor administrative changes to the RMP:
    - Inclusion of COMIRNATY Omicron XBB.1.5, 3 mcg/dose concentrate for dispersion for injection 3-dose vial for 3 mcg (yellow cap) presentation based on outcome of procedure EMEA/H/C/005735/X/0199.
    - Inclusion of COMIRNATY Omicron XBB.1.5 30 micrograms/dose dispersion for injection in glass PFS presentation based on outcome of procedure EMEA/H/C/005735/II/0212/G.
    - Inclusion of JN.1 and KP. 2 strains based on outcome of procedures EMEA/H/C/005735/II/0216 and EMEA/H/C/005735/II/0224 (EMA/VR/0000225514).
    - Removal of PBS-Sucrose and of BA.1 presentations based on outcome of procedure EMEA/H/C/005735/IB/0213/G.
- Editorial changes to streamline the content of the RMP were also performed.

The (main) proposed RMP changes were the following:

RMP Part/Module	RMP v 13.0~~1~~ 2Major Changes
PART I PRODUCT(S) OVERVIEW	
	Editorial changes and inclusion of XBB.1.5 3-dose vial for 3 mcg (yellow cap) and of JN.1 and KP.2 presentations ~~pre-filled syringe (PFS – plastic) presentation~~
PART II SAFETY SPECIFICATION	
PART II Module SI Epidemiology of the Indication(s) and Target Populations	Editorial changes and new updated references related to the new strains ~~XBB.1.5~~ JN.1. and KP.
PART II Module SII Non-Clinical Part of the Safety Specification	~~No~~ Minor changes made.
PART II Module SIII Clinical Trial Exposure	Minor edits and CT tables moved to Annex 7.
PART II Module SIV Populations Not Studied in Clinical Trials	~~No~~ Editorial changes made.
PART II Module SV Post-Authorisation Experience	~~No changes made~~ Updated as of 31 May 2024.
PART II Module SVI Additional EU Requirements for the Safety Specification	No changes made.
PART II Module SVII Identified and Potential Risks	Editorial changes. Post Marketing data from the safety database for the important identified risk of myocarditis/pericarditis updated as of ~~15 Nov 2023~~ 31 May 2024.
PART II Module SVIII Summary of the Safety Concerns	No changes made.
PART III PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)	
III.1 Routine Pharmacovigilance activities.	Editorial changes in Part III.1 and inclusion of ~~pre-filled syringe – PFS (plastic)~~ new presentations.
III.2 Additional Pharmacovigilance Activities and III.3 Summary Table of Additional Pharmacovigilance Activities	Removal of study/milestones for ~~C4591011 and C4591012~~ C4591007, C4591015, C4591024, C4591036, C4591031 (SSE), C4591044, C4591014, WI255886 and C4591051 and milestone updated for study C4591038 and study C4591021, ~~C4591021, C4591022, C4591024, C4591036, C4591051, and C4591052~~ and aPV table text aligned with study C4591048 protocol amendment #5.
PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES	
	No changes made.
PART V PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	
V.1 Routine Risk Minimisation Measures V.2 Additional Risk Minimisation Measures V.3 Summary of Risk Minimisation Measures	Updated based on the changes made in PART III.2.
PART VI PART VI. 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	~~No~~ Editorial changes made. Updated based on the changes made in PART III and V.
PART VII PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	
Annex 2: Updated to remove studies ~~C4591011 and C4591012~~ C4591007, C4591015, C4591024, C4591036, C4591031 (SSE), C4591044, C4591014, WI255886 and C4591051 from the ongoing and planned aPV activities table and milestones updated for study C4591038 and study C4591021 ~~C4591009, C4591021, C4591022, C4591024, C4591036, C4591051 and C4591052~~. Annex 3: Updated to reflect studies ~~C4591011 and C4591012~~ completion/termination. Annex 7: CT tables previously included in Module SIII moved to this annex and vaccination reminder card and label stickers updated. Annex 8: Changes to reflect the updates.	

PRAC Rapporteur comment:

The currently approved version of the RMP is **13.0**, agreed in variation application procedure EMEA/H/C/005735/II/0206/G.

9.1. Safety specification

No changes were made to the Summary of safety concerns:

Table 17. Summary of Safety Concerns

Important Identified Risks	Myocarditis and Pericarditis
Important Potential Risks	None
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
	Long term safety data

9.2. Pharmacovigilance Plan (including post-authorisation safety studies)

9.2.1. Routine Pharmacovigilance Activities

Part III.1 *Routine Pharmacovigilance Activities* has been updated with editorial changes and inclusion of the new presentations.

PRAC Rapporteur comment:

Accepted.

9.2.2. Additional Pharmacovigilance Activities

Part III.2 *Additional Pharmacovigilance Activities* and Part III.3 *Summary Table of Additional Pharmacovigilance Activities* have been updated with:

- removal of the completed studies C4591007, C4591015, C4591024, C4591031 SSE, C4591044, C4591014, WI255886, and C4591051
- milestone change for study C4591038 as per ongoing PAM-MEA-047.5 procedure
- new milestone for final CSR submission of study **C4591021** (see below Assessment of *Justification for the extension of final study report for study C4591021*)

The additional pharmacovigilance studies are summarised in the table below and further detailed in table 64 and table 65 (not reproduced here).

Study Number	Country	Interventional/ non-Interventional/ Low-Interventional	Purpose
~~C4591007~~	~~Global~~	~~Interventional~~	~~Safety~~
~~C4591015~~	~~Global~~	~~Interventional~~	~~Safety~~
~~C4591024[a] (former Safety and immunogenicity in high-risk adults)~~	~~Global~~	~~Interventional~~	~~Safety~~
~~C4591031~~	~~Global~~	~~Interventional~~	~~Safety Effectiveness~~
~~C4591044~~	~~US~~	~~Interventional~~	~~Safety Effectiveness[b]~~
C4591048	US	Interventional	Safety Effectiveness[b]
C4591009	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]~~
~~WI255886~~	~~EU[d]~~	~~Low-Interventional~~	~~Effectiveness[b]~~
C4591036 (former Pediatric Heart Network)	US/CA	Low-Interventional	Safety
~~C4591051~~	~~US~~	~~Non-Interventional~~	~~Safety~~
C4591052	EU	Non-Interventional	Safety

Study Number	Country	Interventional/ non-Interventional/ Low-Interventional	Purpose

~~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.~~

~~Study BNT162-01 was completed and final CSR was submitted on 07 August 2023 (Procedure EMEA/H/C/005735/II/0187).~~

~~Study WI235284 was completed, and final CSR was submitted on 30 June 2023 (Procedure NEMEA/H/C/005735/II/0186/G).~~

~~Study C4591001 was completed, and final CSR is submitted on 09 August 2023 (Procedure EMEA/H/C/005735/II/0188/G).~~

9.2.2.1. Justification for the extension of final study report for study C4591021

The MAH requests a 9-month extension for submission of the final study report for C4591021: Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine.

As noted in protocol amendment version 7.0, (EMEA/H/C/005735/II/0206/G, CHMP Opinion 13 June 2024), the original due date for submission of the final study report was 20 December 2024 with a study completion date (i.e., end of data collection) of 30 September 2024. With the extension being requested, the revised due date for submission of the final study report will be 30 September 2025 with a revised study completion date (i.e., end of data collection) of 31 March 2025.

The reason for requiring this extension is due to the need to collect all necessary data and conduct analyses and quality control checks for the final study report. Whereas all data were extracted, and variables created the end of data collection date (i.e., the availability of the entire final analytical data set) requires further time to complete for the reasons outlined below.

- Validation of anaphylaxis and major congenital anomalies
    - The identification of cases of anaphylaxis and major congenital anomalies can only occur once the Data Expert and Access Partners (DEAPs) run the final, quality-controlled scripts. When these scripts return the patient identification numbers from the matched study cohorts, the DEAPs must then request patient records from healthcare providers, which are necessary for the validation process. Information from the records needs to be extracted to estimate the level of certainty of the cases. Currently, the DEAPs are running the scripts, however, the complex extraction of the information from medical records is still pending collection. It is estimated that an additional 6 months is needed to fully complete this activity.
- Calculation of confidence intervals for the risk differences.
    - Due to resampling of non-vaccinated persons, calculation of 95% confidence intervals for the risk differences requires bootstrapping. Bootstrapping requires repeating the sampling and matching of the cohort 200 times. The size of the Pfizer/BioNTech cohort (approximately 12 million vaccinees) makes this challenging from both software and hardware capacity perspectives. Some of the data sources may need to change their servers due to the large size of the cohort. It is estimated that an additional 6 months is needed to allow sufficient time to complete the calculation of the confidence intervals for the risk differences in all the data sources.

In summary, the MAH requests a 9-month extension for the final study report for C4591021. This extension also requires extending the study completion date by 6 months. The revised due date for submission of the final study report will be 30 September 2025 with a revised study completion date (i.e., end of data collection) of 31 March 2025.

The final study report for C4591021 will be delivered within 6 months of the study completion date, which still enable the MAH to meet the Article 46 regulation.

PRAC Rapporteur comment:

The MAH requests a 9-month extension for the final study report for study C4591021 (formerly named ACCESS/VAC4EU) due to the need to collect all necessary data and conduct analyses and quality control checks for the final study report. According to the MAH all data were extracted, and variables created, however the availability of the entire final analytical data set requires further time to complete. The reasons outlined above are acknowledged. Therefore the final study report submission milestone will be changed from 20 December 2024 to 30 September 2025. Given the argumentation provided by the MAH for the requested extension and the results presented in the previous interim reports (see below), this is accepted.

Study C4591021 background information

Study C4591021, an ongoing non-interventional PASS, is a Comirnaty safety surveillance study conducted in collaboration with University Medical Center Utrecht on behalf of Vaccine Monitoring Collaboration for Europe Consortium research team VAC4EU and based on the master surveillance protocol. The primary study objective is to determine whether an increased risk of prespecified adverse events of special interest (AESI) exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine using two approaches: (i) a cohort design comparing risk in vaccinated and unvaccinated individuals and (ii) a self- controlled risk interval (SCRI) design.

To date, results of the 5th interim report were assessed in MEA 17.9 (AR circulated 16 May 2024) describing the characteristics and incidence rates for 37 AESIs in more than 12 million vaccinated individuals and 12 million matched unvaccinated controls: PRAC Rapporteur concluded that no additional

characterisation of the AESI's were warranted and no new important safety information was identified. Note that in variation application procedure EMEA/H/C/005735/II/0206/G Protocol Amendment (PA) 5, version 7 and SAP Amendment 3, version 5.0 were assessed and considered acceptable (UAR circulated 10 June 2024). In PA#4 (18 October 2023) the final study report milestone was 3 months extended to 20 December 2024.

9.3. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.