22 June 2023
EMA/355553/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on group of variations including an extension of indication

Invented name: COMIRNATY

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

Procedure No. EMEA/H/C/005735/II/0177/G

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
dba	doing business as
DCT	data collection tools
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
Eudra CT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	Food and Drug Administration
FFRNT	fluorescence focus reduction neutralization test
FPFV	first participant first visit
GCP	Good Clinical Practice
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICD	informed consent document
ICF	Informed consent form
ICH	International Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IM	intramuscular
IRB	institutional review board
IRT	interactive response technology
LAR	legally authorized representative
LLOQ	lower limit of quantitation
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
mRNA	messenger RNA
N/A	not applicable
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein binding

NCT	national clinical trial
NT50	50% neutralization titer
OMI	Omicron
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PACL	protocol administrative change letter
PBMC	human peripheral blood mononuclear cells
PD	protocol deviation
PI	Principal Investigator
PT	preferred term
QC	quality control
QTL	quality tolerance limit
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
TME	targeted medical event
US	United States
USA	United State of America
VOC	variant of concern
WHO	World Health Organization
WT	wild-type

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 6 March 2023 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
A.6	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	Type IA	I
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

C.I.6.a: Extension of indication to include Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection and Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection for use as primary vaccination course against COVID-19 in children aged 5 to 11 years and in individuals 12 years of age and older, respectively, based on interim results from studies C4591044 and C4591048. Study C4591044 is an interventional, randomized, 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, while study C4591048 is a phase 1/2/3 master study to investigate the safety, tolerability, and immunogenicity of a bivalent BNT162b2 RNA-based vaccine candidate. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

A.6: To change the ATC Code of tozinameran, riltozinameran and famtozinameran from J07BX03 to J07BN01.

The group of variations requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0466/2022 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0466/2022 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

related to the proposed indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Filip Josephson

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Menno van der Elst

Timetable	Dates
Submission date	06 March 2023
Start of procedure:	25 March 2023
CHMP Rapporteur Assessment Report	22 May 2023
PRAC Rapporteur Assessment Report	26 May 2023
PRAC members comments	31 May 2023
PRAC Outcome	08 June 2023
CHMP members comments	12 June 2023
ETF discussion	13 June 2023
Updated CHMP Rapporteur Assessment Report	15 June 2023
Opinion	22 June 2023

2. Scientific discussion

2.1. Introduction

The data provided in this application are intended to support the authorization for use as a 2 dose primary series of the 10 µg formulation for children 5 to 11 years of age, and the 30 µg formulation for adolescents/adults ≥12 years of age, of the Comirnaty Original/Omicron BA.4-5 Vaccine (also referred to as BNT162b2 Bivalent [WT/OMI BA.4/BA.5] when describing clinical data).

Current authorization of the Comirnaty Original/Omicron BA.4-5 vaccine for individuals ≥5 years of age at the age appropriate dose level of 10 µg or 30 µg was based on extrapolation of safety and immunogenicity data from approximately 1,840 participants >55 years of age in Study C4591031 Substudy E who had a median of at least 1.7 months of follow-up after administration of the Comirnaty Original/Omicron BA.1 vaccine as a fourth dose and supportive data from Study C4591031 Substudy D Phase 3 demonstrating safety, tolerability, and effectiveness of an investigational monovalent Omicron BA.1 vaccine in approximately 640 adult (≥18 to ≤55 years of age) participants up to 1-month post-Dose 4 follow-up. The current authorization was also supported by clinical safety data from primary

and booster vaccination with original BNT162b2 vaccine and post-marketing safety data for original BNT162b2 vaccine.

The MAH now requests authorization of the 10 µg or 30 µg formulation of BNT162b2 Bivalent (Original/OMI BA.4/BA.5) vaccine as a 2-dose primary series in children 5 to 11 years of age (10 µg) and in adolescents/adults ≥12 years of age (30 µg) based upon:

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

2.1.1. Problem statement

Disease or condition

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

Clinical presentation

COVID-19 presentation is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing. However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic patients, disease progression may lead to acute respiratory distress syndrome requiring ventilation, subsequent multi-organ failure, and death.
Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhoea, headache, weakness, and rhinorrhoea. Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.

Management

Currently available therapies have different benefit-risk considerations depending on the stage of illness and disease manifestations. While care for individuals who have COVID-19 has improved with clinical experience, vaccination is the most effective medical countermeasure to decrease risk and mitigate spread of the SARS-CoV-2 virus. There are several vaccines approved for primary vaccination against COVID-19, but most are based on the originally circulating strain. The variant adapted vaccines are so far only approved for booster vaccination.

2.1.2. About the product

At present, BNT162b2 has received temporary authorization for emergency use, conditional marketing approval or full approval in >100 countries globally.

The European Commission (EC) approved the bivalent COMIRNATY Original/Omicron BA.1 vaccine (BNT162b2 Bivalent [WT/OMI BA.1]) and the bivalent COMIRNATY Original/Omicron BA.4-BA.5 vaccine (BNT162b2 Bivalent [WT/OMI BA.4/BA.5]) for use in individuals ≥12 years of age who have received at least primary vaccination against COVID-19 on 01 September 2022 and 12 September 2022, respectively. On 10 November 2022, the 10 µg dose of the COMIRNATY Original/Omicron BA.4-5 vaccine was approved for use in individuals 5 through 11 years of age who have received at least primary vaccination against COVID-19 in EU.

The immunogenicity assessment of a booster vaccination with Original/Omicron BA.4/BA.5 was based on extrapolation of immunogenicity data from booster studies with Comirnaty Original and Original/Omicron BA.1 and explorative non-clinical immunogenicity data for the Original/Omicron BA.4/BA.5.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

2.3. Clinical aspects

2.4. Clinical efficacy

The MAH is seeking to extend the indication of the BNT162b2 Bivalent (WT/OMI BA.4/BA.5), currently only indicated as a booster, to a two dose primary series for children 5-11 years of age (10 µg) and adolescents/adults >12 years of age (30 µg).
No efficacy data from studies examining a two dose primary series for BNT162b2 Bivalent (WT/OMI BA.4/BA.5) were provided. Instead, extrapolation of immunogenicity data from study **C4591044** that investigated this vaccine formulation as a booster (fourth dose) were submitted. The extrapolation is based on participants in Cohort 2 (≥12 years of age) and Cohort 3 (≥18 years of age) in the said study.

In addition, the MAH has provided immunogenicity data from **C4591048** Substudy D, an open-label study that investigates the safety, immunogenicity and tolerability profile of the bivalent BNT162b2 given as a third or fourth dose in participants ≥5 to <12 years of age.

In addition to the submitted data, previous conclusions i.e. the approval of the Original/Omicron BA.1 and Original/Omicron BA.4-5 adapted vaccines as booster doses are taken into account.

2.4.1.1. Study C4591044

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

Table 1. Study C4591044 Cohorts 2 and 3

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

2.4.1.1.1. Immunogenicity Endpoints and Analysis Methods

Table 2. Objectives, Estimands, and Endpoints

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

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

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

a. SAEs are presented from vaccination through 1 month after vaccination in this interim CSR.
b. Seroresponse was defined as achieving a ≥4-fold rise from the baseline (before the study vaccination) at each timepoint after vaccination. If the baseline measurement was below the LLOQ, the postvaccination measure of ≥4 × LLOQ was considered seroresponse.
c. Reference strain was also referred to as the wild type or ancestral strain (Wuhan-Hu-1; USA-WA1/2020).
d. The participants >55 years of age from C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be used as comparator group for this objective.
e. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) and dose group (30 µg, 60 µg) from C4591031 Substudy E expanded cohort who received BNT162b2 Bivalent (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be selected for this objective. The subset selected from C4591031 Substudy E will include similar percentage of participants with baseline positive SARS-CoV-2 infection status as the groups in Cohort 2 of this study, whenever feasible.
f. If the COVID-19 illness visit was conducted as an in-person visit, a blood sample was taken for this assessment. No blood samples were obtained for remote (telehealth) COVID-19 illness visits.

Immunogenicity results were based on validated assays for 50% SARS-CoV-2 neutralizing titers on a newly developed 384-well assay platform (reference strain [USA-WA1/2020, isolated in January 2020], Omicron BA.1, 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 or 60 µg for participants enrolled in this study.

Of note, the 384-well SARS-CoV-2 neutralization assays have been recently validated and, unlike the previously used validated 96-well mNeonGreen SARS-CoV-2 neutralization assay platform, do not use reporter viruses with fluorescent markers. The neutralizing titers between the 384-well platform and 96-well platform are not comparable; the titers from the 384-well assay platform are approximately 2.5-fold higher than those from the 96-well assay platform.

A non-validated fluorescent focus reduction neutralization test (FFRNT) was also used to characterize Omicron BA.4/BA.5, reference strain, and other emerging VOCs (BA.4.6, BA.2.75.2, BQ.1.1, XBB) neutralization responses following a booster (fourth) dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to the WT vaccine (BNT162b2 30 µg) in a subset of BNT162b2-experienced adults 18 through 55 and >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.

2.4.1.1.2. Immunogenicity Population

This part of the immunogenicity analysis included approximately 100 randomized participants per vaccine group (Table 3). Approximately 100 participants in the 18 through 55 and >55 years of age groups in C4591031 Substudy E expanded cohort who received BNT162b2 Bivalent (WT/OMI BA.1) 30 µg or 60 µg were selected as the reference group. To achieve a similar balance of participants with or without prior SARS-CoV-2 infection, except for the 18 through 55 years BNT162b2 Bivalent (WT/OMI BA.1) 60-µg group, the reference group included all evaluable participants with evidence of prior SARS-CoV-2 infection before study vaccination (baseline positive) and randomly selected additional participants without evidence of prior infection (baseline negative) from the corresponding groups in C4591031 Substudy E. Because of substantially lower prior infection rate in C4591031 Substudy E, the subset selected still has a lower baseline infection rate than the groups in C4591044 Cohort 2 except for the 18 through 55 years BNT162b2 Bivalent (WT/OMI BA.1) 60-µg group.

For the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups, the evaluable immunogenicity population for participants with or without evidence of infection up to 1 month after study vaccination included a total of 105 participants 12 through 17 years of age, 95 participants 18 through 55 years of age, and 102 participants >55 years of age (Table 3). Most exclusions from the evaluable immunogenicity population were due to lack of at least 1 valid and determinate immunogenicity result within 28 to 42 days after the study vaccination. The evaluable immunogenicity population without evidence of infection up to 1 month after study vaccination included a total of 25 participants 12 through 17 years of age, 32 participants 18 through 55 years of age, and 40 participants >55 years of age.

For the BNT162b2 Bivalent (WT/OMI BA.1) 30-µg groups from Study C4591031 Substudy E, the evaluable immunogenicity population with or without evidence of infection up to 1 month after study vaccination included a total of 100 participants 18 through 55 years of age and 100 participants >55 years of age (Table 3). The evaluable immunogenicity population without evidence of infection up to 1 month after study vaccination included a total of 67 participants 18 through 55 years of age and 64 participants >55 years of age.

For the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60-µg groups, the evaluable immunogenicity population for participants with or without evidence of infection up to 1 month after study vaccination included a total of 102 participants 18 through 55 years of age, and 99 participants >55 years of age (Table 3). Most exclusions from the evaluable immunogenicity population were due to lack of at least 1 valid and determinate immunogenicity result within 28 to 42 days after the study vaccination. The evaluable immunogenicity population without evidence of infection up to 1 month after study vaccination included a total of 23 participants 18 through 55 years of age and 31 participants >55 years of age.

For the BNT162b2 Bivalent (WT/OMI BA.1) 60-µg groups from Study C4591031 Substudy E, the evaluable immunogenicity population with or without evidence of infection up to 1 month after study vaccination included a total of 100 participants 18 through 55 years of age and 100 participants >55 years of age (Table 3). The evaluable immunogenicity population without evidence of infection up to 1 month after study vaccination included a total of 30 participants 18 through 55 years of age and 65 participants >55 years of age.

Table 3. Immunogenicity Populations – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort

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

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

2.4.1.1.3. Demographic

Demographic characteristics for participants in Cohort 2 with or without evidence of infection up to 1 month after study vaccination in the evaluable immunogenicity population are presented in Table 4.

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

Demographic characteristics for participants without evidence of infection up to 1 month after study vaccination in the evaluable immunogenicity population and for participants with or without evidence of infection up to 1 month after study vaccination in the all-available immunogenicity population were generally similar to those in Table 4.

Table 4. Demographic Characteristics – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

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

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

Abbreviations: N/A = not applicable; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations except for BMI.
b. n = Number of participants with the specified characteristic.
c. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
d. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
e. Month was calculated as 28 days.
f. This value is the denominator for the percentage calculations for BMI.
g. For participants 12 through 15 years of age, obesity is defined as a BMI at or above the 95th percentile from the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 08JAN2023 (21:04)
(Data cutoff date : C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adsl_s005_1m_evl_c2f

Blinding

Cohort 2: Groups with participants ≥18 years of age were observer-blinded at the site level with respect to study intervention allocation (BNT162b2 [WT/OMI BA.4/BA.5]) and open-label to most Pfizer staff.

Administration of the second booster dose was open-label for participants 12 through 17 years of age.

Cohort 3: Both participant groups (18 through 55 years of age and >55 years of age) receiving the second booster were open-label.

Although Cohort 2 had an open-label group (12 through 17 years of age receiving their second booster) and both Cohort 3 groups were open-label, the following instructions for site personnel applied to all participants in order to maintain the blinding for the other cohorts/groups:

In this observer-blind study, the study staff received, stored, dispensed, prepared, and administered the study interventions as unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, were blinded to study intervention assignments. In particular, the individuals who evaluated participant safety were blinded. Because there were differences in physical appearance of the study interventions, the study intervention was administered in a manner that prevents the study participants from identifying the study intervention group based on its appearance.

The PI assigned the responsibility of the unblinded dispensers/administrators to persons who did not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators were assigned per site. Members of the study site staff or clinic pharmacy should fulfil these roles. Contact between the unblinded dispensers and study participants was kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators were not allowed to know the study intervention assigned to any study participant and were not allowed to see the study intervention container contents.

The study will be unblinded to site personnel at a time decided by Pfizer.

2.4.1.1.4. Immunogenicity results

GMT

Omicron BA.4/BA.5 Neutralization

Participants With or Without Evidence of Infection

Omicron BA.4/BA.5 GMTs at pre-vaccination and 1 month after study vaccination in the evaluable immunogenicity population with or without evidence of infection are presented in Figure 1 and Table 14.20. BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 µg and 60 µg dose elicited robust immune response against Omicron BA.4/BA.5 in all age groups and the response was higher than the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups.

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

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

- Higher in participants 12 through 17 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared with other age and vaccine groups at both pre-vaccination and 1 month after vaccination.

- Larger increase from pre-vaccination in participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg and 60-µg groups compared with participants in the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups. The differences between BNT162b2 Bivalent (WT/OMI BA.4/BA.5) groups and BNT162b2 Bivalent (WT/OMI BA.1) were more substantial in the baseline negative groups.

- Generally similar in participants 18 through 55 and >55 years of age who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either dose.

- Higher overall in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60-µg group compared with that in the 30-µg group.

- Generally similar across both sexes within each age and dose group.

Results for participants in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

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

				Vaccine Group (as Randomized)			
				C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		C4591031 BNT162b2 Bivalent (WT/OMI BA.1)	
Assay	Dosage/Age Group	Subgroup	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	30 µg/12-17 years	All	Prevax	104	1105.8 (835.1, 1464.3)	N/A	N/A
			1 Month	105	8212.8 (6807.3, 9908.7)	N/A	N/A
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	78	1791.1 (1379.6, 2325.3)	N/A	N/A
			1 Month	79	9892.5 (8114.6, 12059.8)	N/A	N/A
		Negative[e]	Prevax	26	260.2 (157.1, 430.9)	N/A	N/A
			1 Month	26	4666.1 (3096.1, 7032.2)	N/A	N/A
	30 µg/18-55 years	All	Prevax	95	338.3 (238.1, 480.7)	100	151.5 (113.4, 202.3)
			1 Month	95	2839.0 (2150.0, 3748.8)	100	1072.0 (816.1, 1408.1)
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	62	900.3 (661.5, 1225.2)	33	558.4 (338.6, 920.9)
			1 Month	62	4678.4 (3438.9, 6364.6)	33	2271.4 (1346.7, 3831.2)
		Negative[e]	Prevax	33	53.8 (41.1, 70.5)	67	79.7 (62.7, 101.1)
			1 Month	33	1110.7 (743.9, 1658.4)	67	740.6 (557.2, 984.2)
	30 µg/>55 years	All	Prevax	101	301.9 (215.6, 422.8)	99	225.4 (164.1, 309.6)
			1 Month	102	3019.8 (2327.5, 3918.0)	100	943.4 (733.4, 1213.6)
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	61	745.8 (516.5, 1076.9)	36	948.9 (576.4, 1562.1)
			1 Month	62	4386.5 (3263.2, 5896.4)	36	2334.3 (1524.5, 3574.3)
		Negative[e]	Prevax	40	76.0 (54.7, 105.7)	63	99.1 (78.1, 125.8)
			1 Month	40	1693.1 (1094.0, 2620.1)	64	566.7 (446.2, 719.9)

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

				Vaccine Group (as Randomized)			
				C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		C4591031 BNT162b2 Bivalent (WT/OMI BA.1)	
Assay	Dosage/Age Group	Subgroup	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	30 µg/12-17 years	All	Prevax	105	6863.3 (5587.8, 8430.1)	N/A	N/A
			1 Month	105	23641.3 (20473.1, 27299.8)	N/A	N/A
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	79	8685.4 (7062.7, 10680.9)	N/A	N/A
			1 Month	79	25991.8 (22377.5, 30189.8)	N/A	N/A
		Negative[e]	Prevax	26	3356.2 (2106.9, 5346.2)	N/A	N/A
			1 Month	26	17725.2 (12376.4, 25385.7)	N/A	N/A
	30 µg/18-55 years	All	Prevax	95	2349.0 (1693.4, 3258.4)	100	1338.4 (1056.9, 1695.1)
			1 Month	95	11919.3 (9839.1, 14439.3)	99	6913.9 (5690.4, 8400.5)
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	62	5615.4 (4406.4, 7156.1)	33	3183.8 (2185.4, 4638.2)
			1 Month	62	16214.4 (13340.3, 19707.6)	32	10119.7 (7341.3, 13949.6)
		Negative[e]	Prevax	33	456.8 (291.5, 716.0)	67	873.5 (682.8, 1117.3)
			1 Month	33	6685.8 (4731.8, 9446.9)	67	5763.8 (4550.1, 7301.1)

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

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

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

a. Protocol-specified timing for blood sample collection.

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

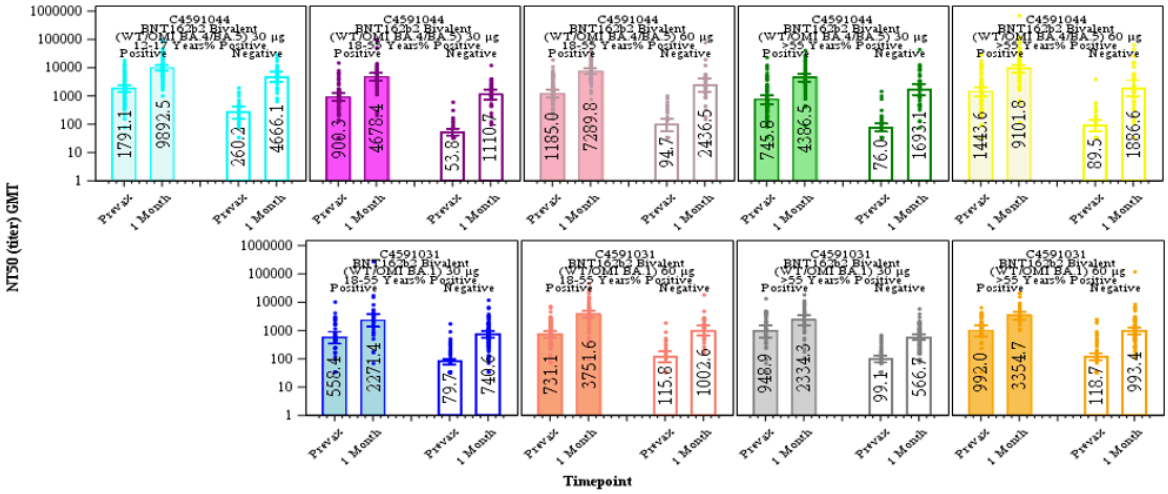
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

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

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

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 08JAN2023 (20:49)
(Data cutoff date : C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022]) Output File: ./nda2 ub1044/C4591044 1MPD C23 CMB/adva s001 gmt sub 1m evl c2f

Figure 1. GMTs and 95% CIs, by Baseline SARS-CoV-2 Status: SARS-CoV-2 Neutralization Assay – Omicron BA.4/BA.5 – NT50 – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



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

Note: Dots represent individual antibody levels.

Note: 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.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 09JAN2023 (00:23)

(Data Cutoff Date: C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022])

Output File: /nda2_ub1044/C4591044_1MPD_C23_CMB/adva_f002_bs_ba4_1m_evl_c2f

Participants Without Evidence of Infection

Omicron BA.4/BA.5 GMTs at pre-vaccination and 1 month after study vaccination in the evaluable immunogenicity population without evidence of infection are presented in Table 5 and Figure 2. The results were similar to the baseline negative groups in the evaluable immunogenicity population with or without evidence of infection described above.

Table 5. Geometric Mean Titers – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

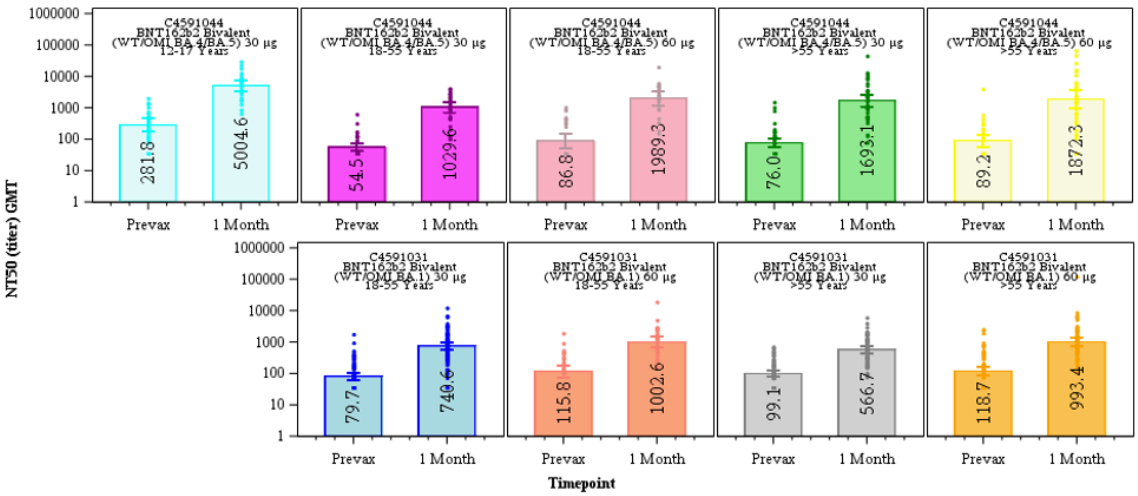
			Vaccine Group (as Randomized)			
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		C4591031 BNT162b2 Bivalent (WT/OMI BA.1)	
Assay	Dosage/Age Group	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	30 µg/12-17 years	Prevax	25	281.8 (171.4, 463.4)	N/A	N/A
		1 Month	25	5004.6 (3353.0, 7469.8)	N/A	N/A
	30 µg/18-55 years	Prevax	32	54.5 (41.3, 71.9)	67	79.7 (62.7, 101.1)
		1 Month	32	1029.6	67	740.6

				(702.6, 1508.9)		(557.2, 984.2)
	60 µg/18-55 years	Prevax	23	86.8 (49.9, 151.1)	30	115.8 (73.7, 181.8)
		1 Month	23	1989.3 (1191.0, 3322.8)	30	1002.6 (672.2, 1495.5)
	30 µg/>55 years	Prevax	40	76.0 (54.7, 105.7)	63	99.1 (78.1, 125.8)
		1 Month	40	1693.1 (1094.0, 2620.1)	64	566.7 (446.2, 719.9)
	60 µg/>55 years	Prevax	31	89.2 (57.5, 138.4)	65	118.7 (86.9, 162.2)
		1 Month	31	1872.3 (952.5, 3680.3)	65	993.4 (746.4, 1322.1)
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	30 µg/12-17 years	Prevax	25	359.1 (215.8, 597.5)	N/A	N/A
		1 Month	25	4009.9 (2602.4, 6178.5)	N/A	N/A
	30 µg/18-55 years	Prevax	32	52.6 (34.0, 81.3)	67	99.3 (75.4, 130.8)
		1 Month	32	910.9 (634.8, 1307.1)	67	1338.6 (998.9, 1793.9)
	60 µg/18-55 years	Prevax	23	92.0 (52.3, 161.9)	30	118.4 (67.5, 207.8)
		1 Month	23	1642.6 (977.5, 2760.2)	30	1378.1 (959.3, 1979.9)
	30 µg/>55 years	Prevax	40	84.7 (55.7, 128.6)	64	114.5 (82.4, 159.3)
		1 Month	40	1481.5 (1020.3, 2151.2)	64	944.7 (746.2, 1196.1)
	60 µg/>55 years	Prevax	29	84.1 (46.0, 153.8)	64	121.8 (85.3, 173.9)
		1 Month	31	1578.2 (983.3, 2532.9)	65	1170.6 (876.3, 1563.8)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	30 µg/12-17 years	Prevax	25	3465.5 (2142.9, 5604.5)	N/A	N/A
		1 Month	25	18432.0 (12794.0, 26554.7)	N/A	N/A
	30 µg/18-55 years	Prevax	32	455.3 (286.2, 724.2)	67	873.5 (682.8, 1117.3)
		1 Month	32	6431.7 (4542.9, 9106.0)	67	5763.8 (4550.1, 7301.1)
	60 µg/18-55 years	Prevax	23	909.7 (512.0, 1616.2)	30	1507.7 (937.0, 2425.9)
		1 Month	23	12277.0 (8444.7, 17848.4)	30	9155.2 (6737.7, 12440.2)
	30 µg/>55 years	Prevax	40	881.9 (601.6, 1292.7)	64	1028.9 (795.8, 1330.3)
		1 Month	40	8386.3	64	5230.2

				(6235.4, 11279.2)		(4357.9, 6277.2)
	60 µg/>55 years	Prevax	31	903.9 (495.1, 1650.0)	65	1482.6 (1102.7, 1993.3)
		1 Month	31	13233.6 (8933.3, 19604.1)	64	7526.8 (5942.0, 9534.4)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; N/A = not applicable; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.
Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 08JAN2023 (20:49)
(Data cutoff date : C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_gmt_1m_wo_evl_c2f

Figure 2. GMTs and 95% CIs: SARS-CoV-2 Neutralization Assay – Omicron BA.4/BA.5 – NT50 – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



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: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.
Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
Note: Dots represent individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 09JAN2023 (00:23)
(Data Cutoff Date: C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022])
Output File: /nda2 ub1044/C4591044 1MPD C23 CMB/adva f002 bad 1m wo evl c2f

Reference Strain Neutralization

Participants With or Without Evidence of Infection

Reference strain GMTs at pre-vaccination and 1 month after study vaccination in the evaluable immunogenicity population with or without evidence of infection are presented in Figure 3.

BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 µg and 60 µg dose elicited robust immune response against reference strain in all age groups and the response was at least similar to the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups.

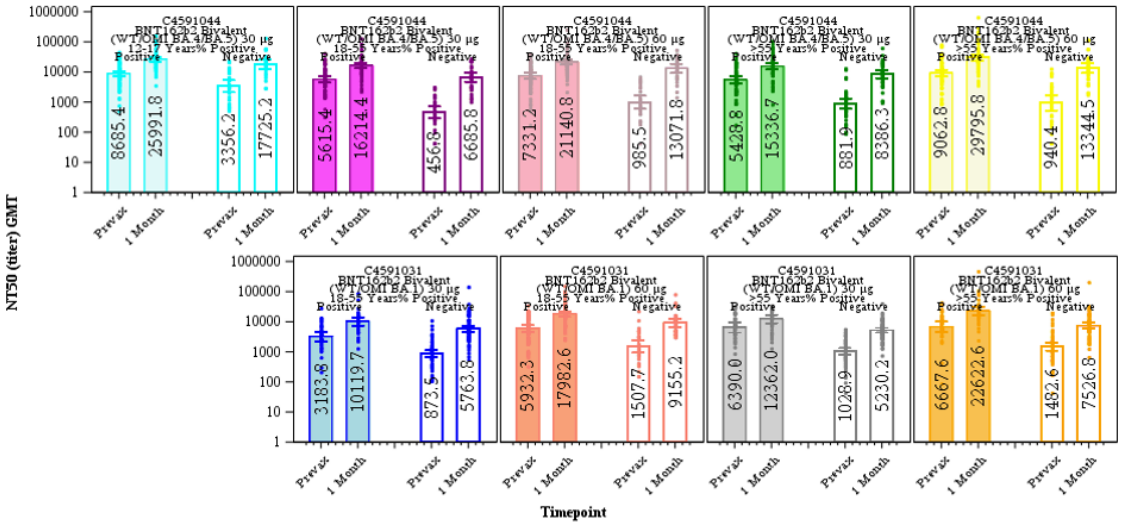
Reference strain GMTs at pre-vaccination and 1 month after study vaccination were higher in participants who were baseline positive compared with those were baseline negative in all age and vaccine groups.

Within baseline positive or baseline negative groups, reference strain GMTs were:

- Higher in participants 12 through 17 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared with other age and vaccine groups at both pre-vaccination and 1 month after vaccination.
- Within baseline negative groups, larger increase from pre-vaccination in participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg and 60-µg groups compared with participants in the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups.
- Within baseline positive groups, similar increase from pre-vaccination in participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg and 60-µg groups compared with participants in the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups.
- Generally similar in participants 18 through 55 and >55 years of age who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either dose.
- Higher overall in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60-µg group compared with that in the 30-µg group.

Figure 3.

5. GMTs and 95% CIs, by Baseline SARS-CoV-2 Status: SARS-CoV-2 Neutralization Assay – Reference Strain – NT50 – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



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

Note: Dots represent individual antibody levels.

Note: 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.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 09JAN2023 (00:23)

Data Cutoff Date: C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022])

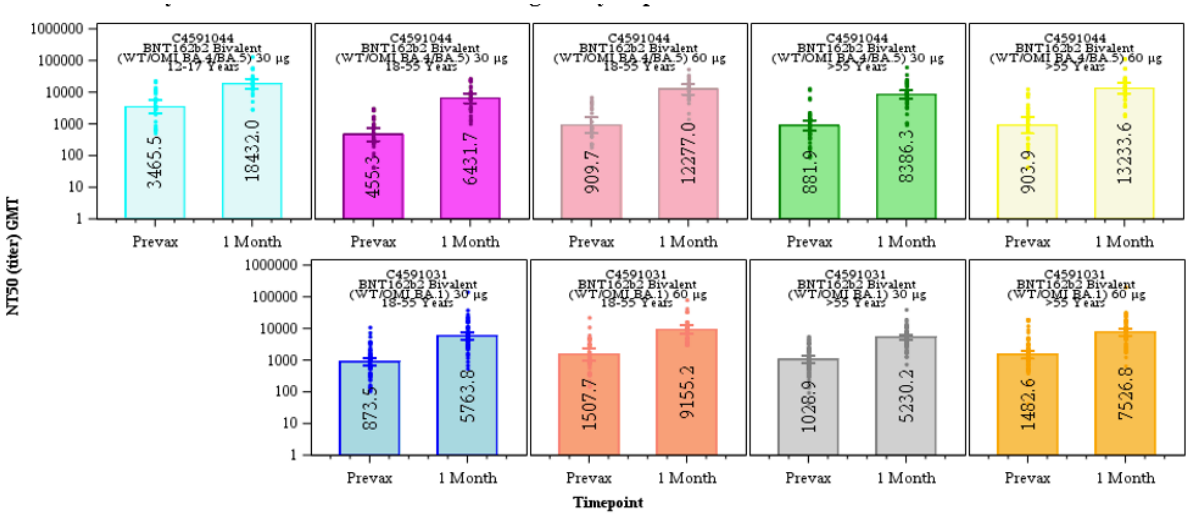
Output File: /nda2_ub1044/C4591044_1MPD_C23_CMB/adva_f002_bs_rf_1m_evl_c2f

Participants Without Evidence of Infection

Reference strain GMTs at pre-vaccination and 1 month after study vaccination in the evaluable immunogenicity population without evidence of infection are presented in Figure 4 (below). The results were similar to the baseline negative groups in the evaluable immunogenicity population with or without evidence of infection described above.

Figure 4.

GMTs and 95% CIs: SARS-CoV-2 Neutralization Assay – Reference Strain – NT50 – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



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

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

Note: Dots represent individual antibody levels.

Note: Number within each bar denotes geometric mean.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 09JAN2023 (00:23)

(Data Cutoff Date: C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022])

Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_f002_rf_1m_wo_evl_c2f

GMFR

Omicron BA.4/BA.5 Neutralization

Participants With or Without Evidence of Infection

BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 µg and 60 µg dose elicited robust immune response against Omicron BA.4/BA.5 in all age groups and the response was higher than the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups.

Omicron BA.1 GMFRs from pre-vaccination to 1 month after study vaccination were higher in participants who were baseline negative compared with those who were baseline positive in all age and vaccine groups.

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

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

- Generally similar between the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30- and 60- µg groups.
- Generally similar across both sexes within each age and dose group.

Results for participants in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Participants Without Evidence of Infection

Omicron BA.4/BA.5 GMFRs from pre-vaccination to 1 month after study vaccination in the evaluable immunogenicity population without evidence of infection up to 1 month after study vaccination are presented in Table 6. The results were similar to the baseline negative groups in the evaluable immunogenicity population with or without evidence of infection described above.

Table 6. Geometric Mean Fold Rises From Before Study Vaccination to Each Subsequent Time Point – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

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

Table 6. Geometric Mean Fold Rises From Before Study Vaccination to Each Subsequent Time Point – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		C4591031 BNT162b2 Bivalent (WT/OMI BA.1)	
Assay	Dosage/Age Group	Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	30 µg/12-17 years	1 Month	25	5.3 (3.7, 7.7)	N/A	N/A
	30 µg/18-55 years	1 Month	32	14.1 (9.1, 22.0)	67	6.6 (5.2, 8.3)
	60 µg/18-55 years	1 Month	23	13.5 (7.9, 23.1)	30	6.1 (3.9, 9.5)
	30 µg/>55 years	1 Month	40	9.5 (6.4, 14.0)	64	5.1 (3.9, 6.5)
	60 µg/>55 years	1 Month	31	14.6 (8.4, 25.5)	64	5.0 (3.7, 6.9)

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

Reference Strain Neutralization

Participants With or Without Evidence of Infection

BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 µg and 60 µg dose elicited robust immune response against reference strain in all age groups and the response was at least similar to the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups.

Reference strain GMFRs from pre-vaccination to 1 month after study vaccination were higher in participants who were baseline negative compared with those were baseline positive in all age and vaccine groups.

Within baseline positive or baseline negative groups, reference strain GMFRs were:

- Within baseline negative groups, lower in participants 12 through 17 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared with other age and vaccine groups, likely due to higher pre-vaccination titers.
- Within baseline positive groups, similar in participants 12 through 17 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared with other age and vaccine groups.
- Within baseline negative groups, higher in participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg and 60-µg groups compared with participants in the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups.
- Within baseline positive groups, similar in participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg and 60-µg groups compared with participants in the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups.
- Generally similar in participants 18 through 55 and >55 years of age who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either dose.
- Generally similar between the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30- and 60-µg groups.
- Generally similar across both sexes within each age and dose group.

Results for participants in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Participants Without Evidence of Infection

Reference strain GMFRs from pre-vaccination to 1 month after study vaccination in the evaluable immunogenicity population without evidence of infection are presented in Table 6. The results were similar to the baseline negative groups in the evaluable immunogenicity population with or without evidence of infection described above.

Seroresponse

Seroresponse was defined as 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).

Omicron BA.4/BA.5 Neutralization

Participants With or Without Evidence of Infection

BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 µg and 60 µg dose elicited robust immune response against Omicron BA.4/BA.5 in all age groups and the response was similar or higher than the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups.

Seroresponse rates at 1 month after study vaccination were lower in participants who were baseline positive compared with those were baseline negative in all age and vaccine groups.

Within baseline positive or baseline negative groups, seroresponse rates at 1 month after study vaccination were:

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

Results for participants in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Participants Without Evidence of Infection

Seroresponse rates at 1 month after study vaccination in the evaluable immunogenicity population without evidence of prior infection are presented in Table 7. The results were similar to the baseline negative groups in the evaluable immunogenicity population with or without evidence of infection described above.

Table 7. Number (%) of Participants Achieving Seroresponse – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		C4591031 BNT162b2 Bivalent (WT/OMI BA.1)	
Assay	Dosage/Age Group	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 – NT50 (titer)	30 µg/12-17 years	1 Month	25	24 (96.0) (79.6, 99.9)	N/A	N/A
	30 µg/18-55 years	1 Month	32	26 (81.3) (63.6, 92.8)	67	47 (70.1) (57.7, 80.7)
	60 µg/18-55 years	1 Month	23	20 (87.0) (66.4, 97.2)	30	19 (63.3) (43.9, 80.1)
	30 µg/>55 years	1 Month	40	36 (90.0) (76.3, 97.2)	63	31 (49.2) (36.4, 62.1)
	60 µg/>55 years	1 Month	31	24 (77.4) (58.9, 90.4)	65	40 (61.5) (48.6, 73.3)
SARS-CoV-2 neutralization assay - Omicron BA.1 – NT50 (titer)	30 µg/12-17 years	1 Month	25	23 (92.0) (74.0, 99.0)	N/A	N/A
	30 µg/18-55 years	1 Month	32	23 (71.9)	67	59 (88.1)

				(53.3, 86.3)		(77.8, 94.7)
	60 µg/18-55 years	1 Month	23	20 (87.0) (66.4, 97.2)	30	22 (73.3) (54.1, 87.7)
	30 µg/>55 years	1 Month	40	37 (92.5) (79.6, 98.4)	64	44 (68.8) (55.9, 79.8)
	60 µg/>55 years	1 Month	29	27 (93.1) (77.2, 99.2)	64	44 (68.8) (55.9, 79.8)
SARS-CoV-2 neutralization assay - reference strain – NT50 (titer)	30 µg/12-17 years	1 Month	25	16 (64.0) (42.5, 82.0)	N/A	N/A
	30 µg/18-55 years	1 Month	32	26 (81.3) (63.6, 92.8)	67	48 (71.6) (59.3, 82.0)
	60 µg/18-55 years	1 Month	23	21 (91.3) (72.0, 98.9)	30	18 (60.0) (40.6, 77.3)
	30 µg/>55 years	1 Month	40	30 (75.0) (58.8, 87.3)	64	35 (54.7) (41.7, 67.2)
	60 µg/>55 years	1 Month	31	24 (77.4) (58.9, 90.4)	64	34 (53.1) (40.2, 65.7)

Abbreviations: LLOQ = lower limit of quantitation; N/A = not applicable; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.
Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 10JAN2023 (20:33) (Data cutoff date : C4591044 [12OCT2022]/C4591031 18-55 Years[25AUG2022]/>55 Years[16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_sero_1m_wo_evl_c2f

Reference Strain Neutralization

Participants With or Without Evidence of Infection

BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 µg and 60 µg dose elicited robust immune response against the reference strain in all age groups and the response was at least similar to the corresponding BNT162b2 Bivalent (WT/OMI BA.1) dose groups.

Seroresponse rates at 1 month after study vaccination were lower in participants who were baseline positive compared with those were baseline negative in all age and vaccine groups.

Within baseline positive or baseline negative groups, seroresponse rates at 1 month after study vaccination were:

- Similar within baseline positive groups and lower within baseline negative groups in participants 12 through 17 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared with other age and vaccine groups.

- Similar or higher in participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg and 60-µg groups compared with the corresponding BNT162b2 Bivalent

(WT/OMI BA.1) age and dose groups. The higher seroresponse rates in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) groups than the BNT162b2 Bivalent (WT/OMI BA.1) groups were more prominent in the baseline negative groups and the >55 years of age group.

- Generally similar in participants 18 through 55 and >55 years of age who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either dose.
- Generally similar in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60-µg group compared with that in the 30-µg group.
- Generally similar across both sexes within each age and dose group.

Results for participants in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Participants Without Evidence of Infection

Seroresponse rates at 1 month after study vaccination in the evaluable immunogenicity population without evidence of prior infection are presented in Table 7. The results were generally similar to the baseline negative groups in the evaluable immunogenicity population with or without evidence of infection described above.

Cohort 2 – New Variants Neutralization Subset

Geometric Mean Titers

Among participants >55 years of age in the evaluable immunogenicity population with or without evidence of prior SARS-CoV-2 infection up to 1 month after the study vaccination GMTs at pre-dose and 1 month post-dose were higher for participants in both vaccine groups in the evaluable immunogenicity population 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 at baseline (baseline negative) (Table 8).

Within both baseline positive or baseline negative groups, Omicron variants BA.4.6, BA.2.75.2, XBB, and BQ.1.1 neutralizing GMTs at 1 month post-dose were higher for participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared with the BNT162b2 30-µg group.

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 variants BA.4.6, BA.2.75.2, BQ.1.1, and XBB were higher in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared to the BNT162b2 Bivalent (WT/OMI/BA.1) 30-µg group. Omicron XBB was the least effectively neutralized variant for both vaccine groups. Despite different intervals from Doses 3 to 4, the pre-Dose 4 neutralizing titers were similar between the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg and BNT162b2 30-µg vaccine groups in participants without evidence of prior SARS-CoV-2 infection up to 1 month after the study vaccination.

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

Table 8. Geometric Mean Titers, by Baseline SARS-CoV-2 Status – New Variants 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 BA.4.6 - NT50 (titer)	All	Prevax	36	91.5 (52.5, 159.7)	40	101.1 (58.9, 173.5)
		1 Month	36	968.2 (623.3, 1503.9)	40	232.2 (149.3, 361.1)
	Positive[d]	Prevax	19	281.6 (159.5, 497.2)	20	283.4 (142.6, 563.2)
		1 Month	19	1564.4 (938.2, 2608.5)	20	586.9 (346.9, 993.0)
	Negative[e]	Prevax	17	26.1 (14.9, 45.6)	20	36.1 (20.4, 63.6)
		1 Month	17	566.3 (280.8, 1142.0)	20	91.9 (59.8, 141.1)
SARS-CoV-2 FFRNT - Omicron BA.2.75.2 - NT50 (titer)	All	Prevax	36	31.1 (20.1, 48.3)	40	48.0 (29.1, 79.0)
		1 Month	36	209.5 (131.6, 333.5)	40	99.3 (62.4, 158.1)
	Positive[d]	Prevax	19	62.0 (32.5, 118.0)	20	125.5 (62.1, 253.9)
		1 Month	19	325.9 (183.0, 580.5)	20	264.5 (146.3, 478.0)
	Negative[e]	Prevax	17	14.4 (10.1, 20.6)	20	18.3 (12.1, 27.7)
		1 Month	17	127.9 (61.5, 265.8)	20	37.3 (25.1, 55.4)
SARS-CoV-2 FFRNT - Omicron BQ.1.1 - NT50 (titer)	All	Prevax	36	30.8 (18.5, 51.3)	40	31.4 (21.4, 45.9)
		1 Month	36	266.5 (171.2, 415.0)	40	58.1 (39.2, 86.1)
	Positive[d]	Prevax	19	74.4 (34.7, 159.4)	20	59.6 (35.0, 101.5)
		1 Month	19	444.4 (259.4, 761.3)	20	132.2 (82.5, 212.0)

Table 9. Geometric Mean Titers, by Baseline SARS-CoV-2 Status – New Variants 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 - NT50 (titer)	Negative[e]	Prevax	17	11.5 (9.2, 14.5)	20	16.5 (11.0, 24.8)
		1 Month	17	150.5 (77.2, 293.4)	20	25.5 (17.4, 37.4)
	All	Prevax	36	18.2 (13.3, 24.8)	40	27.1 (18.9, 38.8)
		1 Month	36	89.8 (60.4, 133.5)	40	41.4 (27.5, 62.3)
	Positive[d]	Prevax	19	26.8 (16.2, 44.2)	20	54.6 (32.5, 92.0)
		1 Month	19	130.9 (80.0, 214.3)	20	98.5 (58.0, 167.3)
	Negative[e]	Prevax	17	11.8 (9.0, 15.4)	20	13.4 (10.3, 17.5)
		1 Month	17	58.9 (31.6, 109.9)	20	17.4 (12.6, 24.1)

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: 08NOV2022 (21:19)
(Data cutoff date : C4591044 [12OCT2022]/C4591031 [16MAY2022]) Output File:
./nda2_ub1044/C4591044_1MPD_C2_NVCMB/adva_s001_gmt_bs_1mnv_evl_c2

Geometric Mean Fold Rises

Overall, in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group, GMFRs from before study vaccination to 1 month post-dose were lower for participants who were baseline positive compared with those who were baseline negative. GMFRs for participants in the BNT162b2 Bivalent

(WT/OMI/BA.1) 30-µg group were generally similar between participants who were baseline positive or baseline negative (Table 10).

Within both baseline positive or baseline negative groups, GMFRs at 1 month post-dose were higher for the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared with the BNT162b2 Bivalent (WT/OMI/BA.1) 30-µg group. Similar results were observed for participants with or without evidence of prior SARS-CoV-2 infection in the all-available immunogenicity population.

In the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, GMFRs of neutralizing titers from before study vaccination to 1 month post-dose for Omicron BA.4.6, BA.2.75.2, BQ.1.1, and XBB were substantially higher for participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared with participants >55 years of age in the BNT162b2 Bivalent (WT/OMI/BA.1) 30-µg group, with higher fold rises reported for Omicron BA.4.6 and BQ.1.1 and lower fold rises reported for Omicron BA.2.75.2 and XBB.

Table 10. Geometric Mean Fold Rises From Before Study Vaccination to Each Subsequent Time Point, by Baseline SARS-CoV-2 Status – New Variants 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]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.4.6 - NT50 (titer)	All	1 Month	36	10.6 (6.7, 16.8)	40	2.3 (1.9, 2.8)
	Positive[d]	1 Month	19	5.6 (3.1, 9.8)	20	2.1 (1.5, 2.8)
	Negative[e]	1 Month	17	21.7 (11.6, 40.5)	20	2.5 (1.9, 3.5)
SARS-CoV-2 FFRNT - Omicron BA.2.75.2 - NT50 (titer)	All	1 Month	36	6.7 (4.3, 10.5)	40	2.1 (1.7, 2.5)
	Positive[d]	1 Month	19	5.3 (2.8, 9.8)	20	2.1 (1.6, 2.7)
	Negative[e]	1 Month	17	8.9 (4.5, 17.5)	20	2.0 (1.6, 2.6)
SARS-CoV-2 FFRNT - Omicron BQ.1.1 - NT50 (titer)	All	1 Month	36	8.6 (5.5, 13.5)	40	1.8 (1.6, 2.2)
	Positive[d]	1 Month	19	6.0 (3.2, 11.2)	20	2.2 (1.8, 2.7)
	Negative[e]	1 Month	17	13.0 (6.9, 24.8)	20	1.5 (1.2, 1.9)
SARS-CoV-2 FFRNT - Omicron XBB - NT50 (titer)	All	1 Month	36	4.9 (3.4, 7.2)	40	1.5 (1.3, 1.8)
	Positive[d]	1 Month	19	4.9 (2.8, 8.5)	20	1.8 (1.5, 2.2)

	Negative[e]	1 Month	17	5.0 (2.8, 8.9)	20	1.3 (1.1, 1.6)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: 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 both the pre-vaccination time point and the given sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 08NOV2022 (20:55)
(Data cutoff date : C4591044 [12OCT2022]/C4591031 [16MAY2022]) Output File:
./nda2_ub1044/C4591044_1MPD_C2_NVCMB/adva_s001_gmfr_1mnv_evl_c2

Seroresponse

Seroresponse was defined as 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).

When comparing the impact of baseline SARS-CoV-2 status, in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group, seroresponse rates at 1 month-post-dose were generally lower for participants who were baseline positive compared with those who were baseline negative. In the BNT162b2 Bivalent (WT/OMI/BA.1)30-µg group, seroresponse rates for participants were higher for participants who were baseline positive compared to participants who were baseline negative (Table 11).

Within the baseline positive or baseline negative group, seroresponse rates at 1 month post- dose were higher for participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared with participants >55 years of age in the BNT162b2 Bivalent (WT/OMI/BA.1) 30-µg group. Similar results were observed for participants with or without evidence of prior SARS-CoV-2 infection in the all-available immunogenicity population.

In the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the proportion of participants who achieved a seroresponse to Omicron BA.4.6, BA.2.75.2, BQ.1.1, and XBB at 1 month post-dose was higher for participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group (94.1%, 70.6%, 76.5%, and 41.2%, respectively) compared with participants >55 years of age in the BNT162b2 30- µg group (15.0%, 5.0%, 0.0%, and 0.0%, respectively).

Table 11. Number (%) of Participants Achieving Seroresponse, by Baseline SARS- CoV-2 Status – New Variants 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]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 FFRNT - Omicron BA.4.6 - NT50 (titer)	All	1 Month	36	27 (75.0) (57.8, 87.9)	40	8 (20.0) (9.1, 35.6)
	Positive[e]	1 Month	19	11 (57.9) (33.5, 79.7)	20	5 (25.0) (8.7, 49.1)
	Negative[f]	1 Month	17	16 (94.1) (71.3, 99.9)	20	3 (15.0) (3.2, 37.9)
SARS-CoV-2 FFRNT - Omicron BA.2.75.2 - NT50 (titer)	All	1 Month	36	24 (66.7) (49.0, 81.4)	40	6 (15.0) (5.7, 29.8)
	Positive[e]	1 Month	19	12 (63.2) (38.4, 83.7)	20	5 (25.0) (8.7, 49.1)
	Negative[f]	1 Month	17	12 (70.6) (44.0, 89.7)	20	1 (5.0) (0.1, 24.9)
SARS-CoV-2 FFRNT - Omicron BQ.1.1 - NT50 (titer)	All	1 Month	36	25 (69.4) (51.9, 83.7)	40	4 (10.0) (2.8, 23.7)
	Positive[e]	1 Month	19	12 (63.2) (38.4, 83.7)	20	4 (20.0) (5.7, 43.7)
	Negative[f]	1 Month	17	13 (76.5) (50.1, 93.2)	20	0 (0.0) (0.0, 16.8)
SARS-CoV-2 FFRNT - Omicron XBB - NT50 (titer)	All	1 Month	36	14 (38.9) (23.1, 56.5)	40	2 (5.0) (0.6, 16.9)
	Positive[e]	1 Month	19	7 (36.8) (16.3, 61.6)	20	2 (10.0) (1.2, 31.7)
	Negative[f]	1 Month	17	7 (41.2) (18.4, 67.1)	20	0 (0.0) (0.0, 16.8)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: 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.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given dose/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.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 08NOV2022 (21:19)
(Data cutoff date : C4591044 [12OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C2_NVCMB/adva_s001_sero_bs_1mnv_evl_c2

Combined Cohort 2 (Group 2 and Group 4) and Cohort 3 – Primary and Secondary Hypotheses

Comparison between BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and BNT162b2 in Participants >55 years of age

Immunogenicity population

The evaluable immunogenicity population for participants with or without evidence of infection up to 1 month after study vaccination included a total of 297 and 286 participants 18 through 55 and >55 years in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups, respectively, and 289 for participants >55 years in the BNT162b2 30-µg group.

Table 12. Immunogenicity Populations – BNT16b2 Bivalent 30- µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30- µg Group of Study C4591031 Substudy E Expanded Cohort

	Vaccine Group (as Randomized)		
	C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		C4591031 BNT162b2 30 µg
	18-55 Years n[a] (%)	>55 Years n[a] (%)	>55 Years n[a] (%)
Randomized[b]	314 (100.0)	306 (100.0)	289 (100.0)
All-available immunogenicity population	302 (96.2)	299 (97.7)	289 (100.0)
Excluded from all-available immunogenicity population	12 (3.8)	7 (2.3)	0
Reason for exclusion[c]			
Participant did not receive study intervention	1 (0.3)	0	0
Did not have at least 1 valid and determinate immunogenicity result after study vaccination	12 (3.8)	7 (2.3)	0
Evaluable immunogenicity population	297 (94.6)	286 (93.5)	289 (100.0)
Participants without evidence of infection up to 1 month after study vaccination[d]	77 (24.5)	105 (34.3)	238 (82.4)
Excluded from evaluable immunogenicity population	17 (5.4)	20 (6.5)	0
Reason for exclusion[c]			
Did not meet eligibility and randomization criteria	6 (1.9)	4 (1.3)	0
Participant did not receive study intervention as randomized	1 (0.3)	0	0
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after study vaccination	16 (5.1)	16 (5.2)	0
Had important protocol deviation	7 (2.2)	6 (2.0)	0

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations.
c. Participants may have been excluded for more than 1 reason.
d. Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 10JAN2023 (20:27)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2 ub1044/C4591044 1MPD C23 CMB/adsl s009 immpop 1m c23

Baseline characteristics

Overall, most participants 18-55 years of age and >55-years in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups combined evaluable immunogenicity population with or without evidence of infection were White (80.5%, 78.3%, respectively), and 87.9% of participants >55 years in the BNT162b2 30-µg group were White. Black or African American participants made up 8.4% and 16.4% of participants 18 through 55 years of age and >55-years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups, respectively, and 6.2% in participants >55 years of age in the BNT162b2 30-µg group (Table 13).There were 13.1% and 12.9% Hispanic/Latino participants 18 through 55 years of age and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups, respectively, and 18.7% of Hispanic/Latino participants >55 years of age in the BNT162b2 30-µg group.

The median age at the time of study vaccination in participants 18 through 55 years of age was 41.0 years and 65.0 years in participants >55 years of age, and the median age was 66.0 years in participants >55 years of age in the BNT162b2 30-µg group.

Female participants made up 65.0% and 54.9% of participants 18 through 55 and >55 years of age, respectively, in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups, and 53.6% of participants >55 years of age in the BNT162b2 30-µg group.

Median time from the last dose of BNT162b2 (received prior to the study) to the study vaccination was approximately 11 months for participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups. For participants >55 years of age in the BNT162b2 30-µg group, the median time from the last dose to the study vaccination was approximately 6 months.

Positive baseline SARS-CoV-2 status made up 71.7% and 61.5% of participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups, respectively, and 14.2% of participants >55 years of age in the BNT162b2 30-µg group.

Table 13. Demographic Characteristics – BNT16b2 Bivalent 30- µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30- µg Group of Study C4591031 Substudy E Expanded Cohort- Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)		
	C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		C4591031 BNT162b2 30 µg
	18-55 Years (N^a=297) n^b (%)	>55 Years (N^a=286) n^b (%)	>55 Years (N^a=289) n^b (%)
Sex			
Male	104 (35.0)	129 (45.1)	134 (46.4)
Female	193 (65.0)	157 (54.9)	155 (53.6)
Race			
White	239 (80.5)	224 (78.3)	254 (87.9)
Black or African American	25 (8.4)	47 (16.4)	18 (6.2)
American Indian or Alaska Native	0	3 (1.0)	0
Asian	30 (10.1)	8 (2.8)	12 (4.2)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	2 (0.7)
Multiracial	3 (1.0)	3 (1.0)	3 (1.0)

Ethnicity			
Hispanic/Latino	39 (13.1)	37 (12.9)	54 (18.7)
Non-Hispanic/non-Latino	256 (86.2)	247 (86.4)	235 (81.3)
Not reported	2 (0.7)	2 (0.7)	0
Age at vaccination (years)			
Mean (SD)	39.2 (9.75)	65.6 (6.74)	66.3 (6.47)
Median	41.0	65.0	66.0
Min, max	(18, 55)	(56, 87)	(56, 87)
Baseline SARS-CoV-2 status			
Positive[c]	213 (71.7)	176 (61.5)	41 (14.2)
Negative[d]	84 (28.3)	110 (38.5)	246 (85.1)
Missing	0	0	2 (0.7)
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (months[e])			
n	297	286	289
Mean (SD)	10.8 (1.65)	11.2 (1.33)	6.8 (1.41)
Median	11.3	11.5	6.3
Min, max	(5.4, 13.0)	(5.5, 12.9)	(5.3, 13.0)
≥5 to <7 Months	13 (4.4)	3 (1.0)	224 (77.5)
≥7 to <9 Months	26 (8.8)	15 (5.2)	40 (13.8)
≥9 to ≤12 Months	184 (62.0)	182 (63.6)	24 (8.3)
>12 Months	74 (24.9)	86 (30.1)	1 (0.3)
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (days)			
n	297	286	289
Mean (SD)	302.8 (46.33)	312.7 (37.16)	190.1 (39.59)
Median	315.0	322.0	175.0
Min, max	(152, 365)	(153, 362)	(147, 365)
<150 Days	0	0	2 (0.7)
150-209 Days	15 (5.1)	6 (2.1)	224 (77.5)
210-269 Days	42 (14.1)	27 (9.4)	47 (16.3)
270-365 Days	240 (80.8)	253 (88.5)	16 (5.5)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	4 (1.3)	6 (2.1)	4 (1.4)
Normal weight (≥18.5-24.9 kg/m^2)	83 (27.9)	63 (22.0)	80 (27.7)
Overweight (≥25.0-29.9 kg/m^2)	97 (32.7)	100 (35.0)	100 (34.6)
Obese (≥30.0 kg/m^2)	113 (38.0)	117 (40.9)	105 (36.3)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
d. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
e. Month was calculated as 28 days.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 05JAN2023 (01:32)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2 ub1044/C4591044 1MPD C23 CMB/adsl s005 1m ev1 c23

Superiority of Anti-Omicron BA.4/BA.5 Immune Response Based on Geometric Mean Ratio

Participants With or Without Evidence of Infection

One of the primary immunogenicity objectives was to assess the superiority with respect to level of Omicron BA.4/BA.5 neutralizing titer induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the

>55-age group relative to the anti-Omicron immune response elicited by BNT162b2 30 µg in the >55-age group from C4591031 Substudy E.

In the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination, model-based GMR of Omicron BA.4/BA.5 neutralizing titer for participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group to C4591031 Substudy E participants >55 years of age in the BNT162b2 30-µg group was 2.91 (2-sided 95% CI: 2.45, 3.44) (Table 14). Superiority of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg to BNT162b2 30 µg in the >55-year age group was met, as the model-based lower bound of the 2-sided 95% CI for GMR was >1. Unadjusted GMR showed similar trends to the model-based GMR.

Results for participants in the all-available immunogenicity population were similar to those in the evaluable immunogenicity population in Table 14.

Table 14. Model-Based Geometric Mean Ratios – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

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

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

Participants Without Evidence of Infection

In the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination, model-based GMR for participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group to C4591031 Substudy E participants >55 years of age in the BNT162b2 30-µg group was 3.37 (2-sided 95% CI: 2.66, 4.29) (Table 15).

Unadjusted GMR showed similar trends to the model-based GMR.

Table 15. Model-Based Geometric Mean Ratios – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)						Vaccine Group Comparison	Age Group Comparison
		C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg		> 55 Years BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg / BNT162b2 30 µg	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg 18-55 Years / >55 Years
		18-55 Years		>55 Years		>55 Years			
Assay	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	GMR[d] (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	1 Month			103	2157.1 (1771.7, 2626.3)	224	639.2 (559.8, 729.8)	3.37 (2.66, 4.29)	
	1 Month	77	1826.3 (1408.4, 2368.3)	103	1820.8 (1454.4, 2279.4)				1.00 (0.71, 1.41)
SARS-CoV-2 neutralization assay -	1 Month			105	11891.3 (10193.5,	236	8518.5 (7695.6,	1.40 (1.16, 1.68)	

reference strain - NT50 (titer)		13872.0)	9429.5)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection)
and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of logarithmically transformed neutralizing titers using a linear regression model with terms of baseline neutralizing titer (log scale) and vaccine group or age group. A separate model was fit for each comparison. Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on the same regression model as stated above.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (01:57)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_gmr_mb_1m_wo_evl_c23

Noninferiority of Anti-Omicron BA.4/BA.5 Immune Response Based on Difference in Seroresponse Rate

The primary immunogenicity objective was also to assess the noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-age group relative to the anti-Omicron BA.4/BA.5 immune response elicited by BNT162b2 30 µg in the >55-age group from C4591031 Substudy E.

Participants With or Without Evidence of Infection

In the evaluable immunogenicity participants with or without prior evidence of infection up to 1 month after study vaccination, 66.7% of participants >55 years of age and 46.5% of participants >55 years of age in the BNT162b2 30-µg group achieved a seroresponse to Omicron BA.4/BA.5. The adjusted difference in percentages of participants in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared with participants given BNT162b2 30 µg as a second booster dose in C4591031 Substudy E was 26.77 % (95% CI: 19.59, 33.95) (Table 16).

Noninferiority based on seroresponse for participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared to participants >55 years of age in the BNT162b2 30 µg was met, as the adjusted lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse was >-5%.

The lower bound of the 2-sided 95% CI for the difference in seroresponse rates was also greater than 0%, indicating a higher seroresponse to Omicron BA.4/5 in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group than in the BNT162b2 30-µg group.

Unadjusted difference in seroresponse rates and 95% CI showed similar trends to the adjusted results.

Differences in seroresponse at 1 month after study vaccination for participants in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Table 16. Adjusted Difference in Percentages of Participants With Seroresponse – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

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

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

Participants Without Evidence of Infection

Differences in seroresponse rate for Omicron BA.4/BA.5 reported for participants in the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination were similar to those in the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination (Table 17).

Unadjusted difference in seroresponse rates showed similar trends to the adjusted results for participants without prior evidence of infection.

Table 17. Adjusted Difference in Percentages of Participants With Seroresponse – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)						Vaccine Group Comparison	Age Group Comparison
		C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg		> 55 Years BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg / BNT162b2 30 µg	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg 18-55 Years / >55 Years
		18-55 Years		>55 Years		>55 Years			
Assay	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	Difference%[e] (95% CI[f])	Difference%[e] (95% CI[f])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	1 Month	77	65 (84.4) (74.4, 91.7)	103	89 (86.4) (78.2, 92.4)	224	113 (50.4) (43.7, 57.2)	32.61 (22.99, 42.23)	-2.43 (-13.21, 8.35)

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 enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
c. n = Number of participants with seroresponse for the given assay at the given sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage.
f. 2-Sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median) for the difference in proportions. The median of baseline neutralizing titers was calculated based on the pooled data in 2 comparator groups.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (01:57)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_dif_mb_1m_wo_evl_c23

Noninferiority of Anti-Reference-Strain Immune Response Based on Geometric Mean Ratio in Participants >55 Years of Age Receiving BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg

The secondary immunogenicity objective was to assess the noninferiority of the anti– reference-strain immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-age group relative to the anti–reference-strain immune response elicited by BNT162b2 30 µg in the >55-age group.

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination, model-based GMR of reference strain neutralization titers for participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group to C4591031 Substudy E participants >55 years of age in the BNT162b2 30 µg was 1.38 (2-sided 95% CI: 1.22, 1.56).

Noninferiority of anti-reference-strain immune response of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 μg to BNT162b2 30 μg in the >55-year age group was met, as the model-based lower bound of the 2-sided 95% CI for GMR was >0.67 (1.5-fold criterion) and the point estimate of the GMR is $\geq$0.8.

Unadjusted GMR showed similar trends to the model-based GMR.

Results for participants in the all-available immunogenicity population were similar to those in the evaluable immunogenicity population.

Participants Without Evidence of Infection

Model-based GMR of reference strain neutralization titers in participants >55 years of age in the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination were similar to those in the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination.

Unadjusted GMR showed similar trends to the model-based GMR.

Comparisons Between Participants 18-55 and >55 Years of Age Receiving BNT162b2 Bivalent (WT/OMI BA.4/BA.5)

Noninferiority of Anti-Omicron BA.4/BA.5 Immune Response in 18 Through 55 Years to >55 Years Based on Geometric Mean Ratio

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination, model-based GMR of Omicron BA.4/BA.5 neutralizing titers for participants 18 through 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group to >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group was 0.98 (2-sided 95% CI: 0.83, 1.16) (Table 14) (above).

Noninferiority of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in participants 18 through 55 years of age to participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group was met, as the model-based lower bound of the 2-sided 95% CI for GMR was >0.67.

Unadjusted GMR showed similar trends to the model-based GMR.

Results for participants in the all-available immunogenicity population were similar to those in the evaluable immunogenicity population in Table 14 (above).

Participants Without Evidence of Infection

In the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination, model-based GMR of Omicron BA.4/BA.5 neutralizing titers for participants 18 through 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group) to participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group was 1.00 (2-sided 95% CI: 0.71, 1.41) (Table 15, above).

Unadjusted GMR showed similar trends to the model-based GMR.

Noninferiority of Anti-Omicron BA.4/5 Immune Response in Participants 18 Through 55 Years to >55 Years Based on Difference in Seroresponse Rate

Participants Without or With Evidence of Infection

In the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination, 61.2% of participants 18 through 55 years and 66.7% of participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups achieved a seroresponse to Omicron BA.4/BA.5. The adjusted difference in percentages of participants with a seroresponse to Omicron BA.4/BA.5 between 18 through 55 years of age and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups was -3.03 % (95% CI: -9.68, - 3.63) (Table 16, above).

Noninferiority based on seroresponse for participants 18 through 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group to participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group was met, as the adjusted lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse was >-10% for the comparison.

Unadjusted difference in seroresponse rates and 95% CI showed similar trends to the adjusted results. However, the unadjusted difference between the 2 age groups was greater than the adjusted difference (with the lower limit of the 2-sided 95% CI for the difference <-10%), likely due to the different proportions of participants who were baseline SARS-CoV-2 positive in the 2 age groups.

Participants Without Evidence of Infection

Differences in seroresponse rate for Omicron BA.4/BA.5 reported for participants 18 through 55 compared with participants >55 years of age in the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination were similar to those in the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination. Unadjusted difference in seroresponse rates showed similar trends to the adjusted results for participants without prior evidence of infection.

Combined Cohort 2 (Group 2 and Group 4) and Cohort 3 – Secondary Descriptive Immunogenicity Objectives – Ages 18 Through 55 and >55 Years of Age

Geometric Mean Titers (Combined Cohort 2 (Group 2 and Group 4) and Cohort 3)

Omicron BA.4/BA.5 Neutralization

Participants With or Without Evidence of Infection

GMTs at pre-dose and 1 month after study vaccination were higher for participants in both vaccine groups in the evaluable immunogenicity population 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) (Table 18, Figure 5)

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

GMTs across both sexes were similar, with higher observed BA.4/BA.5 neutralizing GMTs at 1 month after study vaccination across all age groups and vaccine groups.

Results for participants in the all-available immunogenicity population was similar to the evaluable immunogenicity population.

Table 18. Geometric Mean Titers, by Subgroup – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

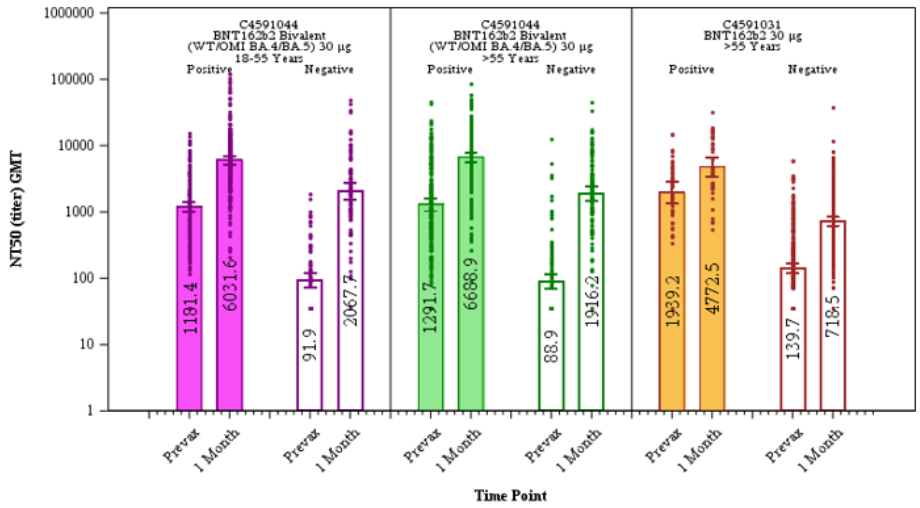
			Vaccine Group (as Randomized)					
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
			18-55 Years		>55 Years		>55 Years	
Assay	Subgroup	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron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

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

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (02:00)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_gmt_sub_1m_evl_c23

Figure 5.

GMTs and 95% CIs, by Baseline SARS-CoV-2 Status: SARS-CoV-2 Neutralization Assay – Omicron BA.4/BA.5 – NT50 – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination - Evaluable Immunogenicity Population



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: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
Note: Dots represent individual antibody levels.
Note: 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.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (04:42)
(Data Cutoff Date: C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022])
Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_f002_bs_ba4_1m_evl_c23

Participants Without Evidence of Infection

Observed Omicron BA.4/BA.5 neutralizing GMTs at 1 month after study vaccination were substantially higher for participants 18 to 55 and >55 years of age without evidence of infection in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups (1872.7 and 1786.9, respectively) compared to participants >55 years of age in the BNT162b2 30-µg group (697.5) in the evaluable immunogenicity population up to 1 month after study vaccination (Table 19, Figure 6).

Table 19. Geometric Mean Titers – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
		18-55 Years		>55 Years		>55 Years	
Assay	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)	Prevax	77	91.1 (69.8, 118.8)	105	83.7 (66.3, 105.7)	228	138.6 (117.1, 164.1)
	1 Month	77	1872.7 (1385.4, 2531.6)	103	1786.9 (1387.4, 2301.5)	232	697.5 (599.7, 811.2)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	Prevax	76	925.2 (681.7, 1255.8)	105	1036.7 (812.6, 1322.5)	236	2043.5 (1734.9, 2407.1)
	1 Month	77	10224.4 (8224.2, 12711.1)	105	10055.9 (8387.0, 12056.9)	238	9150.6 (8161.4, 10259.7)

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

Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.

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

a. Protocol-specified timing for blood sample collection.

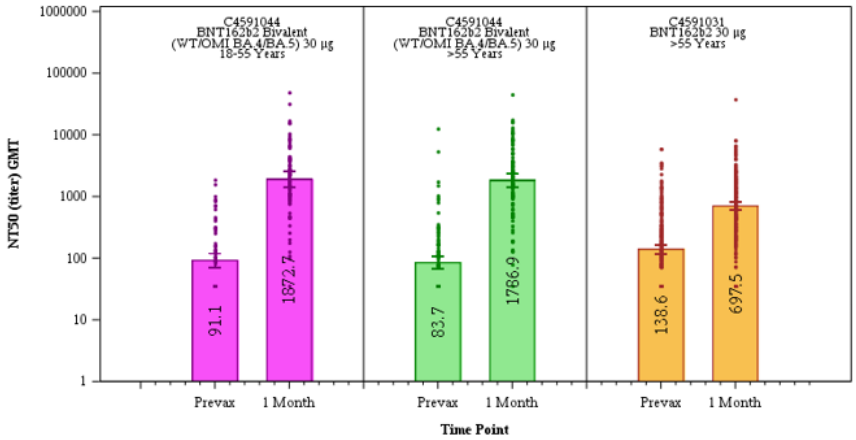
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.

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

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (02:00)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_gmt_1m_wo_evl_c23

Figure 6.

2. GMTs and 95% CIs: SARS-CoV-2 Neutralization Assay – Omicron BA.4/BA.5 – NT50 – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



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

Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.

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

Note: Dots represent individual antibody levels.

Note: Number within each bar denotes geometric mean.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (02:12)

(Data Cutoff Date: C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022])

Output File: /nda2_ub1044/C4591044_1MPD_C23_CMB/adva_f002_ba4_1m_wo_evl_c23

Reference Strain Neutralization

Participants With or Without Evidence of Infection

Similar to Omicron BA.4/BA.5 neutralizing GMT, reference strain GMTs at pre-dose and 1 month after study vaccination were higher for participants who were baseline positive compared with those who were baseline negative for SARS-CoV-2 in all vaccine groups (Figure 7). Reference strain GMTs at 1 month post dose were also higher for all participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups compared with participants 18 through 55 and >55 years of age in the BNT162b2 30-µg groups

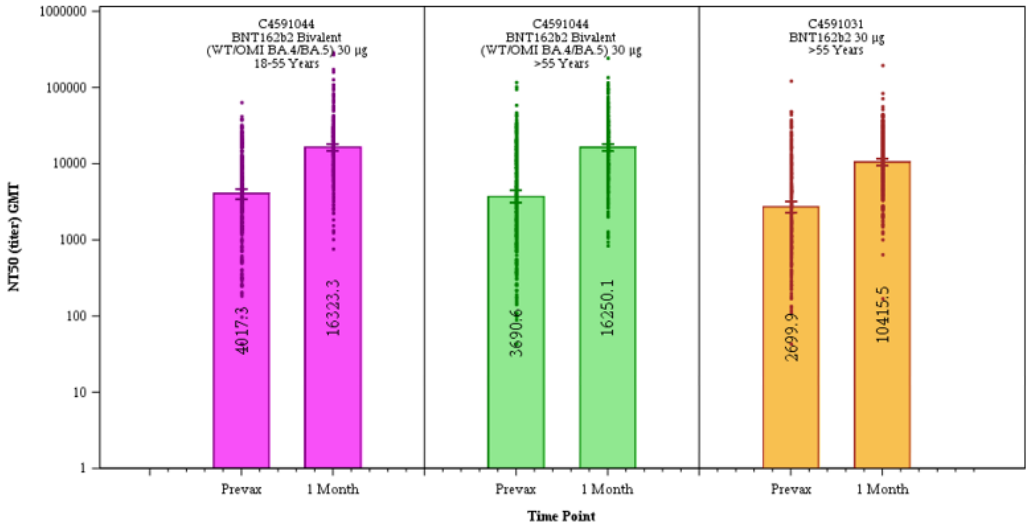
Within baseline positive or negative groups, reference strain neutralizing GMTs at 1 month after study vaccination were higher or similar for the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups compared with the BNT162b2 30-µg group. Reference strain GMTs at 1 month post dose were higher for all participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups compared with participants 18 through 55 and >55 years of age in the BNT162b2 30-µg group, mainly due to higher baseline positive rate in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups.

GMTs across both sexes were similar, with higher observed BA.4/BA.5 neutralizing GMTs at 1 month after study vaccination across all age groups and doses.

Results for participants in the all-available immunogenicity population was similar to the evaluable immunogenicity population.

Figure 7.

GMTs and 95% CIs: SARS-CoV-2 Neutralization Assay – Reference Strain – NT50 – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



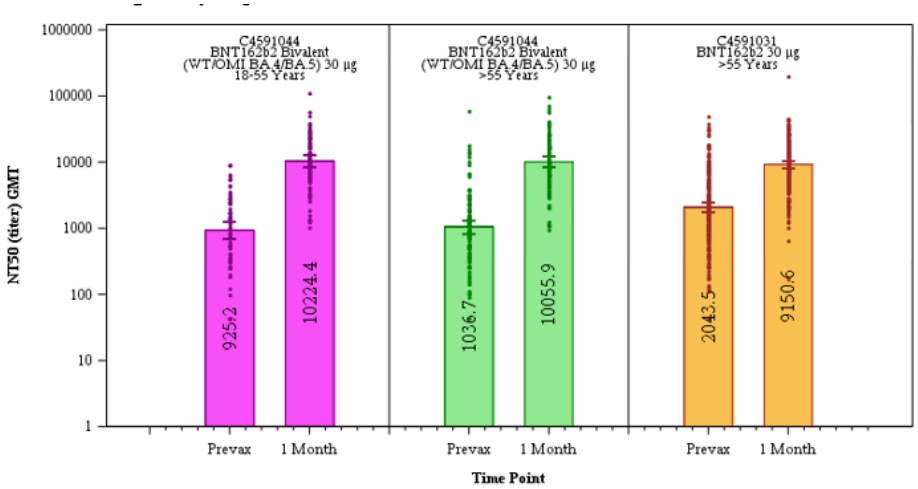
Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
Note: Dots represent individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (02:12)
(Data Cutoff Date: C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022])
Output File: /nda2_ub1044/C4591044_1MPD_C23_CMB/adva_f002_rf_1m_evl_c23

Participants Without Evidence of Infection

The observed reference strain neutralizing GMTs at 1 month after study vaccination were similar for participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups compared with the BNT162b2 30-µg group and were substantially higher than pre-vaccination levels for all age and vaccine groups (Table 19, Figure 8).

Figure 8.

GMTs and 95% CIs: SARS-CoV-2 Neutralization Assay – Reference Strain – NT50 – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



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

Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.

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

Note: Dots represent individual antibody levels.

Note: Number within each bar denotes geometric mean.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (02:12)

(Data Cutoff Date: C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022])

Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_f002_rf_1m_wo_evl_c23

Geometric Mean Fold Rises (Combined Cohort 2 (Group 2 and Group 4) and Cohort 3)

Omicron BA.4/BA.5 Neutralization

GMFRs from before study vaccination to 1 month after study vaccination were higher for participants in both vaccine groups who were baseline negative compared with those who were baseline positive (BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg: 18 to 55 years: 22.5 vs 5.1, >55 years: 21.5 vs 5.2; BNT162b2 30 µg: 5.1 vs 2.4) for SARS-CoV-2 (Table 20). Within baseline positive or baseline negative groups, GMFRs at 1 month after study vaccination were higher for BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups compared with the BNT162b2 30-µg group. GMFRs across both sexes were similarly high across all age groups and doses.

Results for participants in the all-available immunogenicity population was similar to the evaluable immunogenicity population.

Table 20. Geometric Mean Fold Rises From Before Study Vaccination to Each Subsequent Time Point, by Subgroup – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
			18-55 Years		>55 Years		>55 Years	
Assay	Subgroup	Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	All	1 Month	294	7.8 (6.7, 9.2)	282	8.9 (7.5, 10.6)	273	4.6 (4.0, 5.2)
	Baseline SARS-CoV-2 status							
	Positive[d]	1 Month	210	5.1 (4.4, 6.0)	174	5.2 (4.3, 6.3)	39	2.4 (1.8, 3.2)
	Negative[e]	1 Month	84	22.5 (17.1, 29.6)	108	21.5 (16.6, 27.9)	232	5.1 (4.4, 5.9)
	Sex							
	Male	1 Month	103	7.4 (5.6, 9.7)	128	11.3 (8.7, 14.8)	125	4.4 (3.6, 5.4)
	Female	1 Month	191	8.1 (6.6, 9.8)	154	7.3 (5.8, 9.2)	148	4.7 (3.9, 5.6)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	All	1 Month	295	4.1 (3.6, 4.6)	284	4.4 (3.8, 5.1)	287	3.9 (3.4, 4.4)
	Baseline SARS-CoV-2 status							
	Positive[d]	1 Month	212	2.7 (2.4, 3.0)	174	2.7 (2.3, 3.0)	41	1.5 (1.2, 1.9)
	Negative[e]	1 Month	83	11.6 (9.0, 15.0)	110	9.9 (7.8, 12.5)	244	4.5 (4.0, 5.2)
	Sex							
	Male	1 Month	103	4.1 (3.2, 5.1)	129	4.9 (3.9, 6.0)	134	3.9 (3.2, 4.7)
	Female	1 Month	192	4.1 (3.4, 4.8)	155	4.1 (3.4, 5.0)	153	3.9 (3.2, 4.6)

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

Participants Without Evidence of Infection

Overall, in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, GMFRs of neutralizing titers from before study vaccination to 1 month after study vaccination for Omicron BA.4/BA.5 were substantially higher for participants 18 to 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group (20.6 and 21.3, respectively) compared with participants >55 years of age in the BNT162b2 30-µg group (5.0) (Table 21).

Table 21. Geometric Mean Fold Rises From Before Study Vaccination to Each Subsequent Time Point – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
		18-55 Years		>55 Years		>55 Years	
Assay	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)	1 Month	77	20.6 (15.6, 27.1)	103	21.3 (16.5, 27.7)	224	5.0 (4.3, 5.8)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	1 Month	76	11.0 (8.5, 14.2)	105	9.7 (7.6, 12.3)	236	4.5 (3.9, 5.2)

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 05JAN2023 (01:40)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_gmfr_1m_wo_evl_c23

Reference Strain Neutralization

Participants Without or Without Evidence of Infection

GMFRs from before study vaccination to 1 month after study vaccination were generally higher for participants in both vaccine groups who were baseline negative compared with those who were baseline positive (BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg: 18 to 55 years: 11.6 vs 2.7, >55 years: 9.9 vs 2.7; BNT162b2 30 µg: 4.5 vs 1.5) for SARS-CoV-2 reference strain (Table 20, above). Within baseline positive or baseline negative groups, GMFRs at 1 month after study vaccination were higher for BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared with the BNT162b2 30-µg group, possibly due to longer interval from last dose and lower pre-vaccination titers in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group.

GMFR across both sexes were similarly high across all age groups and doses.

Results for participants 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, GMFRs for the reference strain from before study vaccination to 1 month after study vaccination were also higher for participants 18 to 55 and >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group (11.0 and 9.7 respectively) compared with participants >55 years of age in the BNT162b2 30-µg group (4.5) (Table 21, above), possibly due to longer interval from last dose and lower pre-vaccination titers in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group.

GMFRs

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

Seroresponse (Combined Cohort 2 (Group 2 and Group 4) and Cohort 3)

Omicron BA.4/BA.5 Neutralization

Participants Without or Without Evidence of Infection

Seroresponse rates at 1 month after study vaccination were generally higher for participants who were baseline negative compared to those who were baseline positive for SARS-CoV-2 (BNT162b2 Bivalent [WT/OMI BA.4/BA.5] 30 µg: 18 through 55 years: 85.7% vs. 51.4%, >55 years: 86.1% vs. 54.6%; BNT162b2 30 µg: 50.0% vs 28.2%) (Table 22).

Seroresponse rates across both sexes were similar across all age groups and doses.

Results for participants in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

Table 22. Number (%) of Participants Achieving Seroresponse, by Subgroup – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
			18-55 Years		>55 Years		>55 Years	
Assay	Subgroup	Sampling Time Point[a]	N[b]	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	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)
	Baseline SARS-CoV-2 status							
	Positive[e]	1 Month	210	108 (51.4) (44.5, 58.4)	174	95 (54.6) (46.9, 62.1)	39	11 (28.2) (15.0, 44.9)
	Negative[f]	1 Month	84	72 (85.7) (76.4, 92.4)	108	93 (86.1) (78.1, 92.0)	232	116 (50.0) (43.4, 56.6)
	Sex							
	Male	1 Month	103	60 (58.3) (48.1, 67.9)	128	92 (71.9) (63.2, 79.5)	125	60 (48.0) (39.0, 57.1)
	Female	1 Month	191	120 (62.8) (55.6, 69.7)	154	96 (62.3) (54.2, 70.0)	148	67 (45.3) (37.1, 53.7)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	All	1 Month	295	130 (44.1) (38.3, 49.9)	284	130 (45.8) (39.9, 51.8)	287	138 (48.1) (42.2, 54.0)
	Baseline SARS-CoV-2 status							
	Positive[e]	1 Month	212	63 (29.7) (23.7, 36.4)	174	49 (28.2) (21.6, 35.5)	41	5 (12.2) (4.1, 26.2)

	Negative[f]	1 Month	83	67 (80.7) (70.6, 88.6)	110	81 (73.6) (64.4, 81.6)	244	132 (54.1) (47.6, 60.5)
Sex								
	Male	1 Month	103	45 (43.7) (33.9, 53.8)	129	59 (45.7) (36.9, 54.7)	134	64 (47.8) (39.1, 56.6)
	Female	1 Month	192	85 (44.3) (37.1, 51.6)	155	71 (45.8) (37.8, 54.0)	153	74 (48.4) (40.2, 56.6)

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 enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. 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.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 10JAN2023 (20:33)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_sero_sub_1m_evl_c23

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 month after study vaccination was substantially higher for participants 18 through 55 or >55 years of age (84.4% and 86.4%, respectively) compared with participants >55 years of age in the BNT162b2 30-µg group (50.4 %) (Table 23).

Table 23. Number (%) of Participants Achieving Seroresponse – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
		18-55 Years		>55 Years		>55 Years	
Assay	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)	1 Month	77	65 (84.4) (74.4, 91.7)	103	89 (86.4) (78.2, 92.4)	224	113 (50.4) (43.7, 57.2)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	1 Month	76	61 (80.3) (69.5, 88.5)	105	78 (74.3) (64.8, 82.3)	236	127 (53.8) (47.2, 60.3)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the 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.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 10JAN2023 (20:33)
(Data cutoff date : C4591044 Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]/C4591031 [16MAY2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_CMB/adva_s001_sero_1m_wo_evl_c23

Reference Strain Neutralization

Participants Without or Without Evidence of Infection

Seroresponse rates for the reference strain at 1 month -after study vaccination were generally lower for participants who were baseline positive compared to those who were baseline negative for SARS-CoV-2 (BNT162b2 Bivalent [WT/OMI BA.4/BA.5] 30 µg: 18 through 55 years: 29.7% vs. 80.7%, >55 years: 28.2% vs. 73.6%, BNT162b2 30 µg: 12.2% vs 54.1%) (Table 22, above).

Within baseline positive or baseline negative group, seroresponse rates at 1 month after study vaccination were substantially higher for participants 18 through 55 or >55 years in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) than the BNT162b2 µg group.

Seroresponse rates across both sexes were similar across all age groups and doses.

Results for participants 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 month after study

vaccination was substantially higher for participants 18 through 55 or >55 years of age (80.3 % and 74.3%, respectively) compared with participants >55 years of age in the BNT162b2 30-µg group (53.8 %), possibly due to longer interval from last dose and lower pre-vaccination titers in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group (Table 23, above).

2.4.1.2. Study C4591048, substudy D

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

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

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

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

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

2.4.1.2.1. Immunogenicity Endpoints and Analysis Methods

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

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

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

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

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

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

Seroresponse was defined as achieving a ≥4-fold rise from baseline (before the study vaccination [fourth dose]) for participants in Group 2 of Substudy D. If the baseline measurement was below the LLOQ, the postvaccination measure of ≥4 × LLOQ was considered seroresponse. For the comparator group of participants from Study C4591007 Phase 2/3, seroresponse was defined as achieving a ≥4-fold rise from before the third dose. If the pre–third dose measurement was below the LLOQ, the postvaccination measure of ≥4 × LLOQ was considered seroresponse. The exact 2-sided 95% CIs for percentages of participants with seroresponse was calculated using the Clopper-Pearson method.

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

2.4.1.2.2. Immunogenicity Population

A total of 115 participants ≥5 to <12 years of age were assigned to receive a fourth dose with the bivalent BNT162b2 (Original/Omi BA.4/BA.5) at 10 μg (Table 24). Twelve (10.4%) participants were excluded from the evaluable immunogenicity population, most due to not having at least 1 valid and determinate immunogenicity result after vaccination. The evaluable immunogenicity population with or without evidence of infection included 103 (89.6%) participants ≥5 years to <12 years of age who

received a fourth dose with bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg. The evaluable immunogenicity population without evidence of infection included 43 (37.4%) participants in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group.

A total of 113 participants ≥5 to <12 years of age in Study C4591007 Phase 2/3 who received 3 doses of BNT162b2 at 10 µg was selected as the comparator group. No participants were excluded from the evaluable immunogenicity population for the comparator group. To account for potential factors affecting immune response, the comparator group participants were selected from Study C4591007 to have closest match in age and prior SARS-CoV-2 infection status (before Dose 3 for C4591007 participants and before Dose 4 for C4591048 Substudy D participants). As the Dose 3 administration in C4591007 ≥5 to <12 years of age was at least 6 months after Dose 2, the comparator group did not match the prior dosing interval (between Dose 2 and Dose 3 for C4591007 participants and between Dose 3 and Dose 4 for C4591048 participants). The evaluable immunogenicity population with or without evidence of infection for the comparator group included 113 (100%) participants ≥5 years to <12 years of age who received a third dose of BNT162b2 10 µg (Table 24). The evaluable immunogenicity population without evidence of infection included 45 (39.8%) participants in the BNT162b2 group.

Table 24. Immunogenicity Populations – C4591048 Substudy D Group 2 and Study C4591007 Phase 2/3 Participants

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

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

2.4.1.2.3. Demographics of Immunogenicity Population

Demographic characteristics of participants with or without evidence of infection in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups are shown in Table 25. A total of 57.3% of participants in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group were baseline positive at the time of study vaccination (Dose 4). Median time since last dose of BNT162b2 before study vaccination (Dose 4) was 5.5 months in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group. In the BNT162b2 group, 58.4% of participants were baseline positive prior to

Dose 3. Median time between Dose 2 and Dose 3 of BNT162b2 was 6.5 months in the BNT162b2 group.

Demographic characteristics for participants without evidence of infection up to 1 month after study vaccination in the evaluable immunogenicity population and the all-available immunogenicity population with or without evidence of infection were generally similar to those in Table 25.

Table 25. Demographic Characteristics – Participants With or Without Evidence of Infection – C4591048 Substudy D Group2 and Study C4591007 Phase 2/3 Participants – Evaluable Immunogenicity Population

	Vaccine Group (as Assigned/Randomized)	
	C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg (N[a]=103)	C4591007 BNT162b2 10 µg (N[a]=113)
	n[b] (%)	n[b] (%)
Sex		
Male	49 (47.6)	63 (55.8)
Female	54 (52.4)	50 (44.2)
Race		
White	63 (61.2)	91 (80.5)
Black or African American	8 (7.8)	4 (3.5)
Asian	12 (11.7)	11 (9.7)
Native Hawaiian or other Pacific Islander	0	2 (1.8)
Multiracial	17 (16.5)	4 (3.5)
Not reported	3 (2.9)	1 (0.9)
Ethnicity		
Hispanic/Latino	23 (22.3)	16 (14.2)
Non-Hispanic/non-Latino	80 (77.7)	97 (85.8)
Age (years) at Dose 4 (C4591048)/Dose 3 (C4591007)		
Mean (SD)	8.6 (1.65)	8.6 (1.65)
Median	9.0	9.0
Min, max	(5, 11)	(5, 11)
Time (months[c]) from last prior BNT162b2 dose to Dose 4 (C4591048)/Dose 3 (C4591007)		
n	103	113
Mean (SD)	6.0 (1.45)	6.6 (0.31)
Median	5.5	6.5
Min, max	(3.5, 8.5)	(6.3, 7.6)
≥3 to <4 Months	7 (6.8)	0
≥4 to <5 Months	26 (25.2)	0
≥5 to <6 Months	22 (21.4)	0
≥6 to <7 Months	13 (12.6)	99 (87.6)
≥7 to <8 Months	23 (22.3)	14 (12.4)
≥8 to <9 Months	12 (11.7)	0
Time (days) from last prior BNT162b2 dose to Dose 4 (C4591048)/Dose 3 (C4591007)		
n	103	113
Mean (SD)	168.5 (40.51)	185.1 (8.60)
Median	154.0	183.0
Min, max	(98, 239)	(175, 212)
90-240 Days	103 (100.0)	113 (100.0)
Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 status		
Positive[d]	59 (57.3)	66 (58.4)
Negative[e]	44 (42.7)	47 (41.6)
Comorbidities[f]		
Yes	28 (27.2)	33 (29.2)
No	75 (72.8)	80 (70.8)

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

2.4.1.2.4. Immunogenicity results

GMR

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population with or without evidence of prior infection up to 1 month after study vaccination, model-based GMR of Omicron BA.4/BA.5-neutralizing titers for the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group to the BNT162b2 group was 1.12 (2-sided 95% CI: 0.92, 1.37) (Table 26). Unadjusted GMR was 1.57 (2-sided 95% CI: 1.18, 2.09).

Table 26. Model-Based Geometric Mean Ratio - C4591048 Substudy D Group2 (1 Month After Dose 4) to C4591007 Phase 2/3 Participants (1 Month After Dose 3) – With or Without Evidence of Infection - Evaluable Immunogenicity Population

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

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
a. n = Number of participants with valid and determinate assay results for the specified assay at both the given dose and the given sampling time point.
b. GMTs and 2-sided CIs were calculated by exponentiating the LSMeans and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
c. GMRs and 2-sided CIs were calculated by exponentiating the difference of LSMeans for the assay and the corresponding CIs based on the same regression model as stated above.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 02MAR2023 (09:44)
(Data cutoff date: C4591048 Substudy D[25NOV2022]/C4591007[27MAY2022])
Output File: ./nda2_ubped2/C4591048_D_1MPD_1007_Immuno/adva_s004_gmrb_p2_evl

Seroresponse

Omicron BA.4/BA.4 Neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity participants with or without evidence of prior infection up to 1-month postdose, 53.5% of participants in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group achieved seroresponse to Omicron BA.4/BA.5. The adjusted difference in percentages of participants with seroresponse between the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group and the BNT162b2 group was 8.76% (95% CI: -2.47, 19.99) (27). Unadjusted difference in seroresponse rates was 0.79% (95% CI: -12.57, 14.10).

Table 27. Adjusted Difference in Percentages of Participants With Seroresponse Between C4591048 Substudy D Group2 (1 Month After Dose 4) and C4591007 Phase 2/3 Participants (1 Month After Dose 3) – With or Without Evidence of Infection - Evaluable Immunogenicity Population

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

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

GMT

Omicron BA.4/BA.5 neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population with or without evidence of prior infection, for both vaccine groups, GMTs against the Omicron BA.4/BA.5 variant were higher at predose and at 1-month postdose in participants who were baseline positive compared with those who were baseline negative (Table 28, Figure 9).

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

GMTs across both sexes were similar within both vaccine groups.

Table 28. Geometric Mean Titers, by Subgroup–C4591048 Substudy D Group 2 (at Dose 4 and 1 Month After Dose 4) and C4591007 Phase 2/3 Participants (at Dose 3 and 1 Month After Dose 3) – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

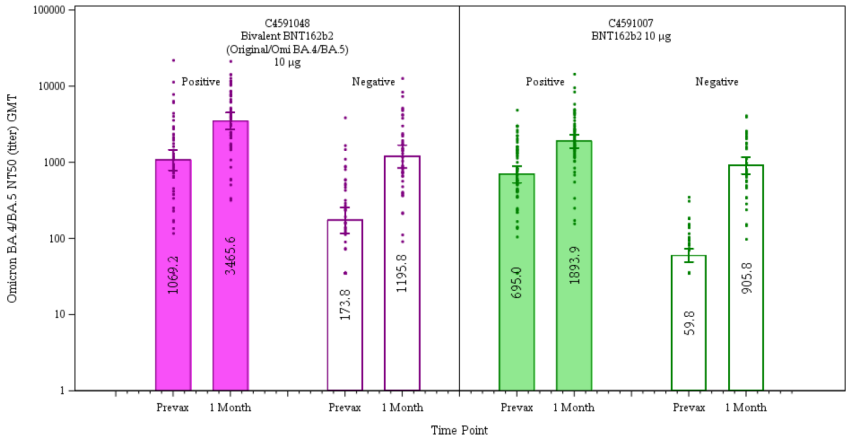
			Vaccine Group (as Assigned/Randomized)			
			C4591048 Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg		C4591007 BNT162b2 10 µg	
Assay	Subgroup	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	Overall	Prevax	102	488.3 (361.9, 658.8)	112	248.3 (187.2, 329.5)
		1 Month	102	2189.9 (1742.8, 2751.7)	113	1393.6 (1175.8, 1651.7)
	Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status[d]					
	Positive	Prevax	58	1069.2 (782.4, 1461.1)	65	695.0 (538.4, 897.3)
		1 Month	58	3465.6 (2682.8, 4476.7)	66	1893.9 (1547.6, 2317.7)
	Negative	Prevax	44	173.8 (117.3, 257.4)	47	59.8 (49.0, 73.1)
		1 Month	44	1195.8 (850.2, 1681.9)	47	905.8 (703.0, 1167.2)
	Sex					
	Male	Prevax	49	608.6 (394.7, 938.4)	62	242.0 (164.1, 356.8)
		1 Month	48	2442.8 (1749.9, 3410.2)	63	1506.8 (1203.1, 1887.2)
	Female	Prevax	53	398.3 (261.5, 606.6)	50	256.5 (167.3, 393.2)
		1 Month	54	1987.2 (1441.3, 2739.8)	50	1263.0 (968.7, 1646.6)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	Overall	Prevax	102	2904.0 (2372.6, 3554.5)	113	1323.1 (1055.7, 1658.2)
		1 Month	102	8245.9 (7108.9, 9564.9)	113	7235.1 (6331.5, 8267.8)

Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status[d]					
Positive	Prevax	58	4198.4 (3342.9, 5272.8)	66	2672.7 (2122.4, 3365.6)
	1 Month	58	9228.4 (7707.0, 11050)	66	7632.5 (6471.6, 9001.5)
Negative	Prevax	44	1786.4 (1305.0, 2445.5)	47	492.9 (390.9, 621.6)
	1 Month	44	7108.8 (5534.0, 9131.8)	47	6711.9 (5345.4, 8427.7)
Sex					
Male	Prevax	49	3369.3 (2480.9, 4575.8)	63	1337.6 (1001.9, 1785.7)
	1 Month	48	8728.6 (6921.6, 11007)	63	7912.0 (6652.6, 9409.9)
Female	Prevax	53	2531.3 (1929.9, 3320.0)	50	1305.1 (902.3, 1887.7)
	1 Month	54	7839.4 (6443.6, 9537.5)	50	6464.1 (5237.5, 7977.9)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive = For C4591048 Substudy D Group 2: positive N-binding antibody result at the Dose 4 visit, positive NAAT result at the Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visit, positive NAAT result at the Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to the Dose 3 visit, or medical history of COVID-19.
Negative = For C4591048 Substudy D Group 2: negative N-binding antibody result at the Dose 4 visit, negative NAAT result at the Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at the Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to the Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 02MAR2023 (09:44)
(Data cutoff date: C4591048 Substudy D[25NOV2022]/C4591007[27MAY2022])
Output File: ./nda2_ubped2/C4591048_D_1MPD_1007_Immuno/adva_s001_gmt_p2_evl

Figure 9.

Geometric Mean Titer and 95% CIs by Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status: SARS-CoV-2 Neutralization Assay – Omicron BA.4/BA.5 – NT50 (Titer) – C4591048 Substudy D Group 2 (at Dose 4 and 1 Month After Dose 4) and C4591007 Phase 2/3 Participants (at Dose 3 and 1 Month After Dose 3) – With or Without Evidence of Infection – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 g 90 to 240 days prior to enrollment.
Note: Dots represent individual antibody levels.
Note: Number within each bar denotes geometric mean.
Note: Positive = For C4591048 Substudy D Group 2: positive N-binding antibody result at the Dose 4 visit, positive NAAT result at the Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visit, positive NAAT result at the Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to the Dose 3 visit, or medical history of COVID-19. Negative = For C4591048 Substudy D Group 2: negative N-binding antibody result at the Dose 4 visit, negative NAAT result at the Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at the Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to the Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 02MAR2023 (09:45) Data cutoff date: C4591048 Substudy D[25NOV2022]/C4591007[27MAY2022]
Output File: ./nda2 ubped2/C4591048 D 1MPD 1007 Immuno/adva f002 sars 50 by eval

Reference Strain Neutralization

Participants With or Without Evidence of Infection

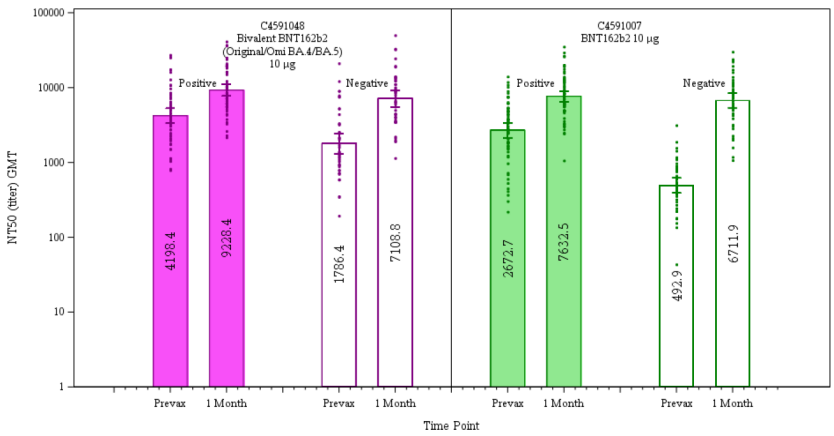
In the evaluable immunogenicity population with or without evidence of prior infection, for both vaccine groups, the observed reference strain GMTs were higher at predose and generally similar or higher at 1 month postdose in participants who were baseline positive compared with those who were baseline negative (Table 28, Figure 10).

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

GMTs across both sexes were similar within both vaccine groups.

Figure 10.

Geometric Mean Titer and 95% CIs by Baseline (Dose 4 C4591048/Dose 3 C4591007) SARS-CoV-2 Status: SARS-CoV-2 Neutralization Assay – Reference Strain – NT50 (Titer) – C4591048 Substudy D Group 2 (at Dose 4 and 1 Month After Dose 4) and C4591007 Phase 2/3 Participants (at Dose 3 and 1 Month After Dose 3) – With or Without Evidence of Infection – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 g 90 to 240 days prior to enrollment.
Note: Dots represent individual antibody levels.
Note: Number within each bar denotes geometric mean.
Note: Positive = For C4591048 Substudy D Group 2: positive N-binding antibody result at the Dose 4 visit, positive NAAT result at the Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visit, positive NAAT result at the Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to the Dose 3 visit, or medical history of COVID-19. Negative = For C4591048 Substudy D Group 2: negative N-binding antibody result at the Dose 4 visit, negative NAAT result at the Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at the Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to the Dose 3 visit, and no medical history of COVID-19.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 02MAR2023 (09:45) Data cutoff date: C4591048 Substudy D[25NOV2022]/C4591007[27MAY2022]
Output File: /nda2 ubped2/C4591048 D 1MPD 1007 Immuno/adva f002 ref 50 by eval

Participants Without Evidence of Infection

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

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

GMFR

Omicron BA.4/BA.5 neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity populations with or without evidence of prior infection, for both vaccine groups, GMFRs of Omicron BA.4/BA.5 at 1-month post dose were higher in participants who were baseline negative compared with those who were baseline positive (bivalent BNT162b2 [Original/Omi BA.4/BA.5]: 6.9 vs 3.3, BNT162b2: 15.1 vs 2.7) (Table 29).

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

GMFRs across both sexes were similar within both vaccine groups.

Participants Without Evidence of Infection

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

Reference Strain Neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity populations with or without evidence of infection, for both vaccine groups, GMFRs of reference strain at 1-month postdose were higher for participants who were baseline negative compared with those who were baseline positive (bivalent BNT162b2 [Original/Omi BA.4/BA.5]: 4.0 vs 2.2, BNT162b2: 13.6 vs 2.9) (Table 29).

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

GMFRs across both sexes were similar within both vaccine groups.

Participants Without Evidence of Infection

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

Table 29. Geometric Mean Fold Rises by Subgroup–C4591048 Substudy D Group 2 (From Dose 4 to 1 Month After Dose 4) and C4591007 Phase 2/3 Participants (From Dose 3 to 1 Month After Dose 3) – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

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

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

Seroresponse

Omicron BA.4/BA.5 neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population with or without evidence of prior infection, seroresponse rates at 1-month postdose were generally higher for participants who were baseline negative compared with those who were baseline positive (bivalent BNT162b2 [Original/Omi BA.4/BA.5]: 75.0% vs. 36.8%, BNT162b2: 89.4% vs 26.2%) (Table 30).

For baseline positive groups, seroresponse rates at 1-month postdose were slightly higher in participants in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) compared with the BNT162b2 group. For baseline negative groups, seroresponse rates at 1-month postdose were slightly lower in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) compared with the BNT162b2 group (Table 30).

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

Participants Without Evidence of Infection

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

Reference Strain Neutralization

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population with or without evidence of prior infection, seroresponse rates at 1-month postdose were higher for participants who were baseline negative compared to those who were baseline positive (bivalent BNT162b2 [Original/Omi BA.4/BA.5]: 47.7% vs. 17.5%, BNT162b2: 95.7% vs 25.8%) (Table 30).

For baseline positive participants, seroresponse rates at 1-month postdose were generally similar in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups. For baseline negative participants, seroresponse rates were lower in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with the BNT162b2 group, which relate to the higher pre-vaccination titers in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group (Table 30).

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

Participants Without Evidence of Infection

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

Table 30. Number (%) of Participants With Seroresponse, by Subgroup–C4591048 Substudy D Group 2 (at 1 Month After Dose 4) and C4591007 Phase 2/3 Participants (1 Month After Dose 3) – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

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

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

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

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

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

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

2.4.2. Discussion on clinical efficacy

This application concerns the extension of indication of the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) to a two dose primary series for children 5-11 years of age (10 µg) and adolescents/adults >12 years of age (30 µg). The product received a booster indication for these age groups in the autumn of 2022. There were no clinical immunogenicity data submitted for that approval. Non-inferior immune responses to bivalent Original/Omicron BA.1 were demonstrated compared to the original vaccine against the reference strain, along with superior immune responses to the BA.1 strain when given as booster dose. The approval of bivalent Original/Omicron BA.4/5 was based on the assumption that this bivalent vaccine would have the same characteristics as the bivalent Original/Omicron BA.1 vaccine as booster.

No data on primary vaccination with a bivalent vaccine are available and are not expected in the age groups concerned in this application since the vast majority of the world population is either already vaccinated or exposed to the virus.

In the current application, immunogenicity data from **study C4591044**, where the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) was given as the fourth dose (second booster) in participant ≥12 years of age, and study **C4591048 Substudy D**, which investigated the immunogenicity of the bivalent product given as a third or fourth dose in participants ≥5 to <12 years of age. The results were compared to a control group given the original vaccine as a third dose in a separate study. As discussed by the MAH above, the comparator group may not be ideal, as the exposure to infection appears to be lower in the comparator group than the test group.

In study C4591044 the MAH reports a clear increase in neutralizing GMT and a positive GMFR to both Omicron BA.4/5 and the reference strain in all age groups 1 month post-vaccination (12-17 years n = 105, 18-55 years n = 297, >55 years n = 284). GMTs across both sexes were similar. Thus, the booster capacity of the product is confirmed.

In the age group >18 years old, groups from the previous study C4591031 were employed as comparators. C4591031 investigated the immunogenicity of the original Comirnaty and the other bivalent formulation BNT162b2 Bivalent (WT/OMI BA.1) given as the fourth dose. The BNT162b2 Bivalent (WT/OMI BA.4/BA.5) consistently performed better with regard to eliciting neutralizing antibody titers against both Omicron BA.4/5 as well as the reference strain when compared to BNT162b2 Bivalent (WT/OMI BA.1) and the original formulation.

The validity of the comparison of the bivalent Original/Omicron BA.4-5 to the original or Original/OmicronBA.1 was questioned as it was unclear why the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) performed better with regards to neutralization and seroresponse rate for Omicron BA.1 and the reference strain in comparison to the other two formulations. The MAH explained that linear regression model-based analysis adjusting the baseline neutralising titre level has been used to overcome the problem with incomparable historic control. GMR originates from model based GMT calculation, which is considered as an intermediate estimate in order to reach a more valid and meaningful model-based GMR.

The superiority criterium for BNT162b2 Bivalent (WT/OMI BA.4/BA.5) in neutralization of Omicron BA.4/5 in comparison to the original BNT162b2 in the age group >55 years were met: GMR 2.91 (2-sided 95% CI: 2.45, 3.44). The model-based lower bound of the 2-sided 95% CI for GMR was >1, thus the criteria for superiority were met. The non-inferiority criterium for BNT162b2 Bivalent (WT/OMI BA.4/BA.5) were also met with regard to the anti-omicron BA.4-5 seroresponse rate in the age group >55 years. The secondary immunogenicity objective to show noninferiority of the anti–reference-strain immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) relative to the anti–reference-strain immune response elicited by BNT162b2 30 µg in the >55-age group was also met. The MAH showed also non-inferiority in anti-omicron BA.4/5 GMR and seroresponse rate in the 18-55 years of age compared to the >55 years group in participants who received the bivalent vaccine.

It is noteworthy that when the immunogenicity of the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) against new variants in participants >55 years of age (*n = 36*) was investigated, the results were diverse. While a reasonable increase in neutralizing titers were observed against Omicron BA.4.6 1 month post-vaccination, the effect against BQ.1.1, BA.2.75.2 and XBB was very low, and even lower against XBB. Although these *in vitro* analyses do not represent the full immune response elicited *in vivo*, which is likely more potent, it was noted that the neutralization effect against emerged variants is notably reduced.

With regard to the younger cohort ≥5 to <12 years of age, the primary immunogenicity objectives of **C4591048 Substudy D** were to descriptively compare the anti-Omicron BA.4/BA.5 immune response in participants who received 3 prior doses of BNT162b2 10 µg and received bivalent BNT162b2 as a fourth dose to participants in study C4591007 who received the third dose of the original BNT162b2 10

µg. The secondary objectives were to describe the immune response elicited by bivalent BNT162b2 in the same cohort with regard to GMT and GMFR of reference strain- and omicron BA.4/5-neutralizing antibody titers.

The model-based GMR comparing bivalent BNT162b2 (Original/Omi BA.4/BA.5) with BNT162b2 in neutralization of Omicron BA.4/5 is close to 1 (1.12 (2-sided 95% CI: 0.92, 1.37)), meaning no substantial difference between the different vaccine formulations. Unadjusted GMR was 1.57 (2-sided 95% CI: 1.18, 2.09). The seroresponse rate to omicron BA.4/5 was also almost identical: 53.5% vs 52.7% for the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and the original BNT162b2, respectively. The seroresponse rate to the reference strain overall is reported to be lower in the BNT162b2 (Original/Omi BA.4/BA.5) vaccinated group as compared to the group that received the original BNT162b2: 30.7% vs 54.9%. In the evaluable immunogenicity population without evidence of prior infection, the proportion of participants who achieved seroresponse at 1-month postdose were 48.8% in the bivalent BNT162b2 (Original/Omi BA.4/BA.5) group compared with 95.6% in the BNT162b2 group. It is however noted that the first group generally had a higher baseline level of GMT due to having one extra dose.

The rise of GMT levels to Omicron BA.4/BA.5 for baseline negative participants are very similar post-vaccination for both formulation, albeit the bivalent vaccine elicited a slightly stronger response in baseline positive participants. The same analysis conducted on the reference strain yielded similar results. It can be concluded that the bivalent Original/Omicron BA.4-5 vaccine is capable of eliciting a booster response in 5-<12 year old subjects.

2.4.1. Conclusions on clinical efficacy

In summary the data submitted in this application demonstrate:

- A substantial increase in GMT to Omicron BA.4/5 and the reference strain is seen after the bivalent BNT162b2 (Original/Omi BA.4/BA.5) is administered as a booster in all age groups.
- In the age group >18 years, the immune response against Omicron BA.4/5 is more substantial compared to the original formulation.
- In the age group 12-17 years there is a lack of an active comparator.
- In the age group 5-11 years the bivalent vaccine does not perform substantially better than the original vaccine formulation with regards to neutralization of Omicron BA.4/5 according to the model-based GMR.

Considering that:

- Bivalent Original/Omicron BA.1 has demonstrated superior immune responses to BA.1 and non-inferior responses to the reference strain
- Any bivalent original/variant vaccine is considered to have similar characteristics as the Original/Omicron BA.1 vaccine
- Booster responses of the same magnitude can be extrapolated to primary vaccination
- No primary vaccination data will be available
- It is likely that primary vaccination with a vaccine covering currently circulating strains is superior against these, compared to primary vaccination with the original vaccine

- In the dose-finding study C4591001 for the original formulation, it was shown that 10 µg of mRNA encoding the spike antigen elicited a somewhat comparable response as the 30 µg formulation in healthy adults.

it seems acceptable to agree on a primary vaccination schedule for the bivalent vaccine. In totality, it is reasonably likely that a primary series with the bivalent BNT162b2 (Original/Omi BA.4/BA.5) will yield a better, or comparable, immune response as the original formulation against the strains investigated.

2.5. Clinical safety

With the aim to support the use of the bivalent COVID-19 vaccine Original/Omicron BA.4-5 administered as a primary series at 10µg (5+5µg) for subjects aged ≥5 to <12 years and at 30µg (15+15 µg) in subjects ≥12 years of age, data from two studies (C4591048 substudy D and C4591044) has been presented where these vaccines have been administered as booster dose to each age group. The studies are described separately below. No data has been provided where the bivalent vaccine has been used as primary series.

Study C4591048 Substudy D Group 2 (≥5 to <12 Years of Age): Booster (Fourth Dose) with BNT162b2 Bivalent (Original/Omicron BA.4-5) at 10 µg

Substudy D is an open-label study to evaluate the safety, tolerability, and immunogenicity of a fourth dose of the bivalent BNT162b2 (Original/Omicron BA.4-5) at 5+5 µg in participants ≥5 to <12 years of age who have received 3 prior doses of BNT162b2 Original at 10 µg. Data cut-off was 25 November 2022.

Initially, 115 participants ≥5 years to <12 years were assigned to receive a fourth dose of the bivalent BNT162b2 Original/ BA.4-5 at 10 µg. Two participants were excluded from the safety population as they withdrew prior to receiving study intervention, therefore the safety population included 113 subjects that had received a fourth dose. At the cut-off date 106 subjects had completed the 1-month post-study vaccination visit. Median follow-up time after study vaccination was 1.6 months.

Demographics

Table 31. Demographic Characteristics – Substudy D Group 2 – Safety Population

	Vaccine Group (as Administered)
	Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg (N[a]=113) n[b] (%)
Sex	
Male	57 (50.4)
Female	56 (49.6)
Race	
White	66 (58.4)

Black or African American	9 (8.0)
Asian	13 (11.5)
Multiracial	22 (19.5)
Not reported	3 (2.7)
Ethnicity	
Hispanic/Latino	23 (20.4)
Non-Hispanic/non-Latino	90 (79.6)
Age at the study vaccination (years)	
Mean (SD)	8.6 (1.65)
Median	9.0
Min, max	(5, 11)
Time (months[c]) from Dose 3 of BNT162b2 (received prior to the study) to the study vaccination	
n	113
Mean (SD)	6.0 (1.46)
Median	5.5
Min, max	(2.6, 8.5)
<3 Months	1 (0.9)
≥3 to <4 Months	7 (6.2)
≥4 to <5 Months	29 (25.7)
≥5 to <6 Months	24 (21.2)
≥6 to <7 Months	13 (11.5)
≥7 to <8 Months	27 (23.9)
≥8 to <9 Months	12 (10.6)
Time (days) from Dose 3 of BNT162b2 (received prior to the study) to the study vaccination	
n	113
Mean (SD)	167.6 (40.93)
Median	154.0
Min, max	(73, 239)
<90 Days	1 (0.9)
90-240 Days	112 (99.1)
Obese[d]	
Yes	10 (8.8)
No	103 (91.2)
Baseline SARS-CoV-2 status	
Positive[e]	66 (58.4)
Negative[f]	47 (41.6)
Comorbidities[g]	
Yes	31 (27.4)
No	82 (72.6)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Month was calculated as 28 days.
d. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
e. Positive N-binding antibody result at the study vaccination visit, positive NAAT result at the study vaccination visit, or medical history of COVID-19.
f. Negative N-binding antibody result at the study vaccination visit, negative NAAT result at the study vaccination visit, and no medical history of COVID-19.
g. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR Morb Mortal Wkly Rep. 2020;69(32):1081-8 and/or obesity (BMI ≥ 95th percentile).
PFIZER CONFIDENTIAL SDTM Creation: 08DEC2022 (18:48) Source Data: adsl Table Generation: 15DEC2022 (21:18) (Data cutoff date : 25NOV2022 Database snapshot date : 08DEC2022) Output File:

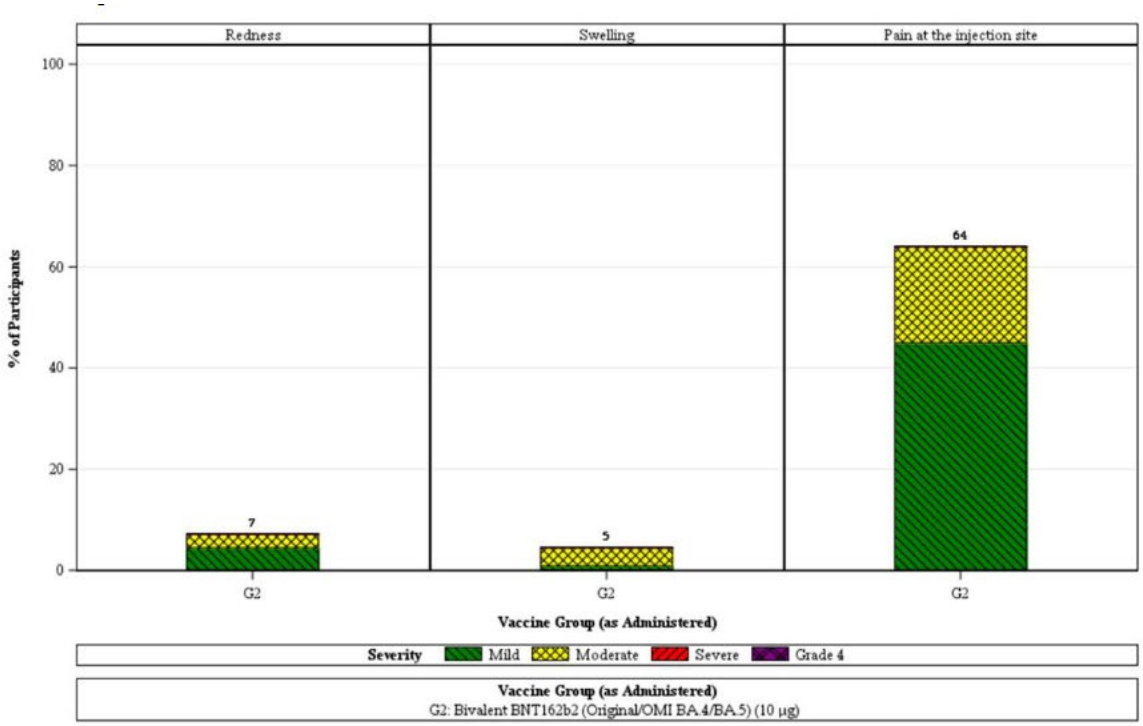
Ten participants received a non-study vaccine (Influenza vaccine) after study vaccination. Nine participants received the influenza vaccine at least 14 days after study vaccination, as allowed per protocol; 1 participant received the influenza vaccine 12 days after study vaccination.

Local Reactions

All local reactions illustrated in the figure below were mild or moderate in severity. No severe or Grade 4 local reactions were reported.
The median onset for all local reactions was 1 to 2 days, and all events resolved within a median duration of 2 days after onset.
No clinically meaningful differences in local reactions were observed by sex or baseline SARS-CoV-2 status subgroups.

Figure 11.

Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Substudy D Group 2 – Safety Population



Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
Note: The number above each bar denotes the percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 08DEC2022 (18:49) Source Data: adfacevd
Table Generation: 15DEC2022 (14:38) (Cutoff Date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: /nda2_ubped2/C4591048_D_1MPD_Safety/adce_f001_lr_p2_12

Systemic Events

The reported systemic events are illustrated in the figure below. Two (1.8%) participants reported fever >38.9°C to 40°C. No participants reported fever >40.0 °C. Antipyretic or pain medication use was reported by 23.4% of participants after study vaccination.

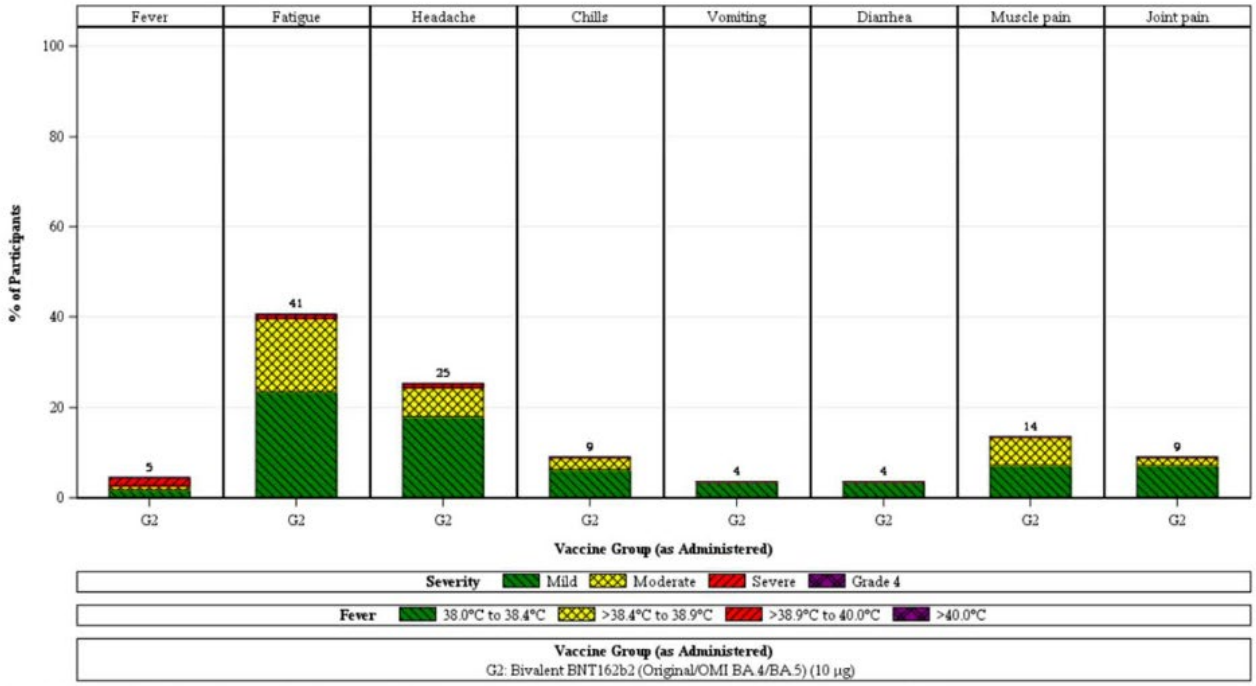
Most systemic events were mild or moderate in severity. Incidence of severe systemic events was low (fatigue and headache, 1 participant [0.9%] each) in the ≥5 years to <12 years of age group who received a fourth dose of the bivalent BNT162b2 (Original/Omi BA.4/BA.5) at 10 µg. No Grade 4

systemic events were reported. The median onset for all systemic events was 2 to 4 days, and all events resolved within a median duration of 1 to 2 days after onset.

No clinically meaningful differences in systemic events were observed by sex or baseline SARS-CoV-2 status subgroups.

Figure 12.

Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Substudy D Group 2 – Safety Population



Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
Note: Severity was not collected for use of antipyretic or pain medication.
Note: The number above each bar denotes the percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 08DEC2022 (18:49) Source Data: adfacevd
Table Generation: 15DEC2022 (14:38) (Cutoff Date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: /nda2_ubped2/C4591048_D_1MPD_Safety/adce_f001_se_p2_12

Adverse Events

In total, 4 (3.5%) participants reported any AE. Related AEs and severe AEs were reported by 1 (0.9%) participant each. No SAEs or life-threatening AEs were reported. No withdrawals due to AEs, or deaths were reported. Overall, the AE profile at 1 month post dose was generally similar to that at 7 days post dose. No additional AEs were reported up to data cut-off date of 25 November 2022.

Table 32. Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination to 1 Month After the Study Vaccination, by System Organ Class and Preferred Term – Substudy D Group 2 – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg (N[a]=113) n[b] (%)	(95% CI[c])
Any adverse event	4 (3.5)	(1.0, 8.8)
Infections and infestations	2 (1.8)	(0.2, 6.2)
Influenza	1 (0.9)	(0.0, 4.8)
Otitis media	1 (0.9)	(0.0, 4.8)
Investigations	1 (0.9)	(0.0, 4.8)
Lymph node palpable	1 (0.9)	(0.0, 4.8)
Respiratory, thoracic and mediastinal disorders	1 (0.9)	(0.0, 4.8)
Oropharyngeal pain	1 (0.9)	(0.0, 4.8)

Note: MedDRA (v25.1) coding dictionary applied.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 08DEC2022 (18:48) Source Data: adae Table Generation: 15DEC2022 (14:49) (Data cutoff date : 25NOV2022 Database snapshot date : 08DEC2022) Output File: ./nda2_ubped2/C4591048_D_1MPD_Safety/adae_s150_1md2_soc_p2_12

Immediate Adverse Events

No participant in the ≥5 years to <12 years of age group were reported to have an immediate AE within 30 minutes of study vaccination.

Related Adverse Events

AEs assessed by the investigator as related were reported by 1 participant and included 1 event of lymph node palpable.

Severe or Life-Threatening Adverse Events

One participant reported a severe AE, and no participant reported a life-threatening AE or SAE from study vaccination through 1 month after study vaccination.

Adverse Events Leading to Withdrawal

There were no discontinuations due to AEs reported for participants in Group 2 from study vaccination through 1 month after vaccination.

Other Significant Adverse Events

Some AEs are of specific interest due to their autoimmune or neuroinflammatory nature, theoretical association with vaccines, or known occurrence in patients with COVID-19. From study vaccination through 7 days post dose, no AEs of anaphylaxis/hypersensitivity, appendicitis, Bell's palsy, myo/pericarditis were reported up to 1 month post vaccination in these 113 participants. AEs of clinical interest that were identified in the safety database from study vaccination to 1 month after study vaccination are summarized below:

Lymphadenopathy: Lymphadenopathy is considered an adverse reaction to this vaccine and is noted as such in the product labelling. One male participant between 10 and 17 years of age reported an event of lymph node palpable (left axillary lymph node palpable) of moderate severity with onset on Day 2 after study vaccination that resolved within 3 days. The event was assessed by the investigator as related to study intervention.

MAH Safety Conclusion:

The safety profile within 1 month after study vaccination (dose 4) with the bivalent BNT162b2 (Original/Omicron BA.4/BA.5) at the 10-µg dose level was generally well tolerated, with mostly mild or moderate reactogenicity and few reported AEs. No new adverse reactions were identified based on the available data from this data cut.
The reactogenicity profile within 7 days after the bivalent BNT162b2 (Original/Omicron BA.4/BA.5) vaccine was generally similar to that previously observed in association with the original BNT162b2 vaccine within the respective age group.
The AE profile within 1 month after study vaccination was consistent with the known safety profile of BNT162b2. Incidence of AEs, including severe AEs, was low. No immediate AEs, SAEs, or AEs leading to withdrawal were reported. Other than 1 case of lymph node palpable, no other AEs of clinical interest were reported (eg, anaphylaxis/hypersensitivity, appendicitis, Bell's palsy, myo/pericarditis). No new or concerning safety findings were noted in these 113 participants up to 1 month of post vaccination data.
Based on the safety data up to 1 month after study vaccination with the bivalent BNT162b2 (Original/Omicron BA.4/BA.5) at the 10-µg dose levels in 113 Study C4591048 participants ≥5 years to <12 years of age, the BA.4-5 Omicron-modified bivalent vaccine appears to be safe and tolerable in this population, and consistent with the known safety profile of BNT162b2.

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

This study was previously evaluated in EMEA/H/C/005735/X/0147 with a cut-off date 12 Sept 2022 and in EMEA/H/C/005735/MEA/059.1 with similar cut-off date (12 Oct 2022) as in this application.

In Cohort 2, he safety population included 528 participants ≥12 years of age who received a fourth dose of BNT162b2 bivalent (Original/Omicron BA.4-5) 30- or 60-µg as illustrated in the table below. Duration of follow-up and vaccine administration are also illustrated below. All but 1 randomized participant received the study vaccination. In total, in participants ≥12 years of age who received a booster dose of BNT162b2 bivalent 30-or 60-µg, all but 1 (99.8%) completed the 7-day post-dose vaccination visit, and all but 9 (98.3%) completed the 1-month post-dose vaccination visit. One (0.9%) participant in the 18 to 55 years of age group who received BNT162b2 bivalent 60-µg was withdrawn from the study (due to physician decision) as of the data cut-off date (12 October 2022).

Table 33. Follow-up Time After Study Vaccination – Cohort 2 – 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) n[b] (%)	30 µg (N[a]=103) n[b] (%)	60 µg (N[a]=110) n[b] (%)	30 µg (N[a]=106) n[b] (%)	60 µg (N[a]=102) n[b] (%)	Total (N[a]=528) n[b] (%)
Participants (%) with length of follow-up of:						
<1 Month	0	0	1 (0.9)	0	0	1 (0.2)
≥1 Month to <2 Months	107 (100.0)	103 (100.0)	109 (99.1)	106 (100.0)	102 (100.0)	527 (99.8)
Mean (SD)	1.6 (0.13)	1.6 (0.10)	1.6 (0.14)	1.6 (0.10)	1.6 (0.10)	1.6 (0.12)
Median	1.5	1.6	1.6	1.6	1.6	1.6
Min, max	(1.3, 1.8)	(1.3, 1.8)	(0.6, 1.8)	(1.3, 1.8)	(1.3, 1.8)	(0.6, 1.8)

Note: Follow-up time was calculated from the study vaccination to the cutoff date or withdrawal date, whichever date was earlier.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 26OCT2022 (16:03) Source Data: adsl Table Generation: 26OCT2022 (22:39) (Data cutoff date : 12OCT2022 Database snapshot date : 25OCT2022) Output File:

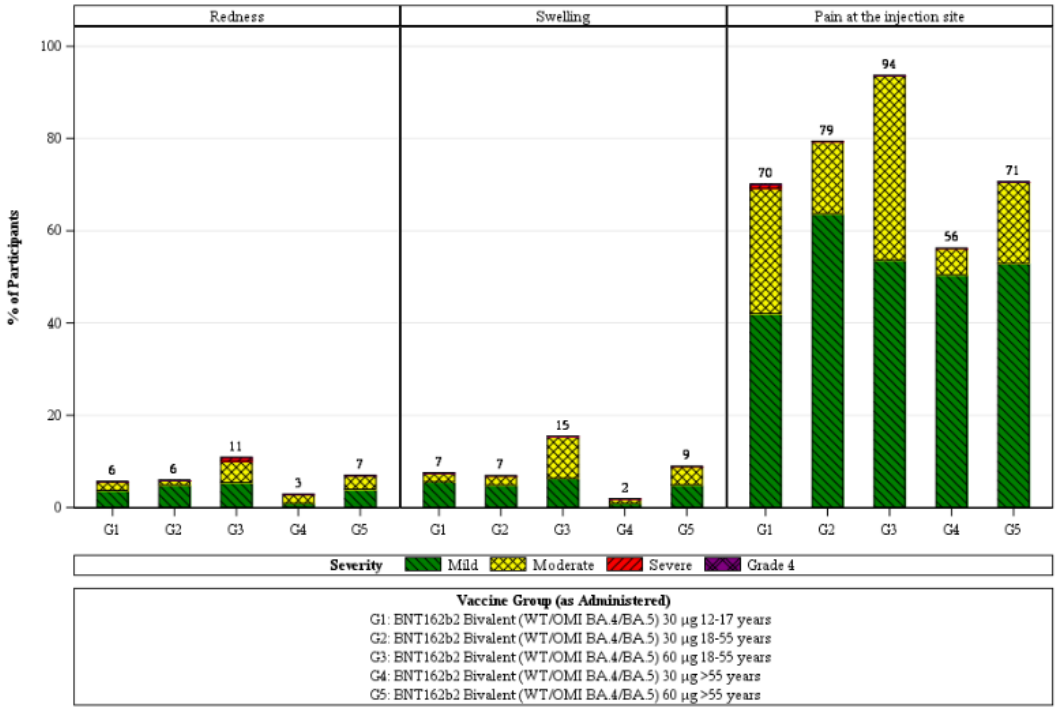
Local Reactions

Local reactions and systemic events recorded in the e-diary for 7 days post vaccination are summarized in the figure below.

Most local reactions were mild or moderate in severity. Severe local reactions were reported by 1 (0.9%) participant in the 12 to 17 years of age group who received a booster dose of BNT162b2 bivalent 30-µg (severe pain at injection site) and 1 (0.9%) participant in the 18 to 55 years of age group who received a booster dose of BNT162b2 bivalent 60-µg (severe redness at injection site). No Grade 4 local reactions were reported in any group. The median onset for all local reactions was 1 to 3 days, and all events resolved within a median duration of 1 to 3 days after onset.
The pattern of local reactions reported within 7 days after the BNT162b2 bivalent (WT + OMI BA.4/BA.5) vaccine was generally similar to those previously observed in association with an Omicron BA.1-modified BNT162b2 bivalent vaccine and to the original BNT162b2 vaccine within the respective age groups. At each dose level, the frequency of reactions tended to be lower in the participants >55 years of age. No clinically meaningful differences in local reactions were observed by sex or baseline SARS-CoV-2 status subgroups.

Figure 13.

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



Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 26OCT2022 (16:04) Source Data: adfacevd Table Generation: 26OCT2022 (22:28)
(Data Cutoff Date: 12OCT2022, Database Snapshot Date: 25OCT2022) Output File: /nda2_ub1044/C4591044_1MPD_C2/adce_f001_lr_1m_c2

Systemic Events

The incidence and/or severity of most systemic events was higher in participants who received the 60-µg dose level of BNT162b2 bivalent within each age group.

Most systemic events were mild or moderate in severity. In the BNT162b2 bivalent 30-µg dose group, severe systemic events of fever (n=1), fatigue (n=3), and diarrhoea (n=1) were reported. In the BNT162b2 bivalent 60-µg dose group, severe systemic events of fever (n=4), fatigue (n=5), headache (n=2), chills (n=1), muscle pain (n=2), and joint pain (n=2) were reported. No Grade 4 systemic events were reported in any group.

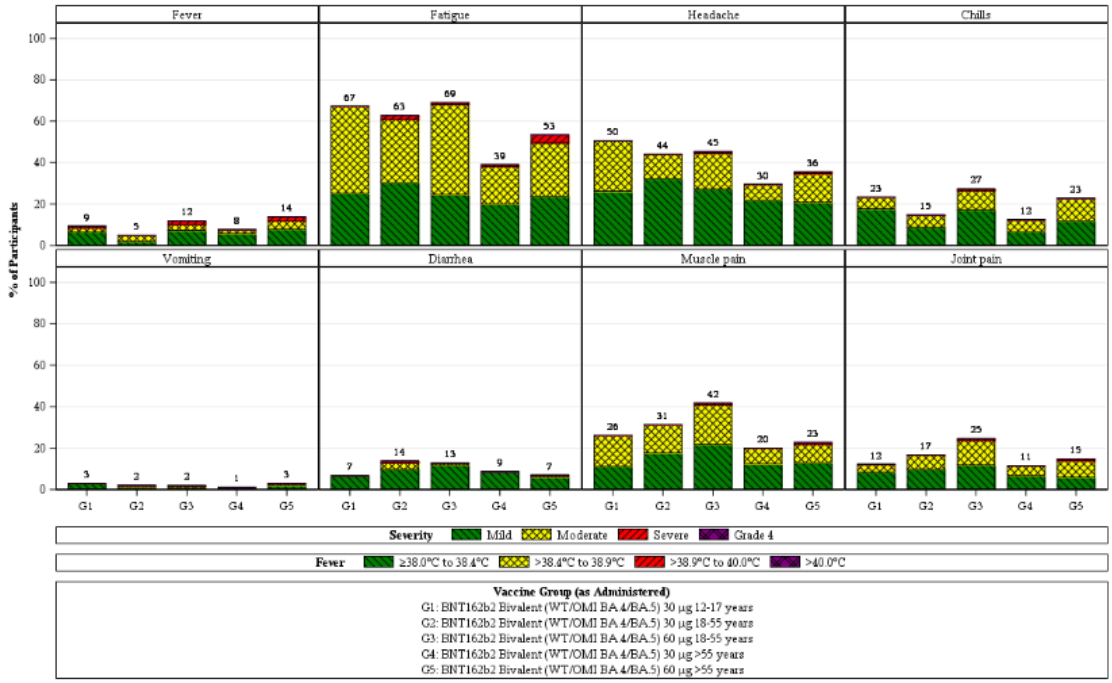
The median onset for all systemic events was 2 to 4 days, and all events resolved within a median duration of 1 to 2 days after onset.

The pattern of systemic events reported within 7 days after the BNT162b2 bivalent (WT + OMI BA.4/BA.5) vaccine was generally similar to those previously observed in association with an Omicron BA.1-modified BNT162b2 bivalent vaccine and to the original BNT162b2 vaccine within the respective age groups. At each dose level, the frequency of events tended to be lower in the participants >55 years of age.

No clinically meaningful differences in systemic events were observed by sex or baseline SARS-CoV-2 status subgroups.

Figure 14.

Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Cohort 2 – Safety Population



Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 26OCT2022 (16:04) Source Data: adfacevd Table Generation: 26OCT2022 (22:28)
(Data Cutoff Date: 12OCT2022, Database Snapshot Date: 25OCT2022) Output File: /nda2_ub1044/C4591044_1MPD_C2/adce_f001_se_1m_c2

Adverse Events

Table 34. Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination. Through 1 Month after the Study Vaccination – Cohort 2 – 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=107)	30 µg (N=103)	60 µg (N=110)	30 µg (N=106)	60 µg (N=102)
Adverse Event	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any adverse event	8 (7.5)	3 (2.9)	9 (8.2)	4 (3.8)	7 (6.9)
Related[c]	6 (5.6)	1 (1.0)	3 (2.7)	1 (0.9)	1 (1.0)
Severe	0	0	0	1 (0.9)	0
Life-threatening	0	0	0	0	0
Any serious adverse event	0	0	0	1 (0.9)	0
Related[c]	0	0	0	0	0
Severe	0	0	0	1 (0.9)	0
Life-threatening	0	0	0	0	0
Any nonserious adverse event	8 (7.5)	3 (2.9)	9 (8.2)	4 (3.8)	7 (6.9)
Related[c]	6 (5.6)	1 (1.0)	3 (2.7)	1 (0.9)	1 (1.0)
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Any adverse event leading to withdrawal	0	0	0	0	0
Related[c]	0	0	0	0	0
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Death	0	0	0	0	0

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to the study intervention.
PFIZER CONFIDENTIAL SDTM Creation: 26OCT2022 (16:03) Source Data: adae Table Generation: 26OCT2022 (22:47) (Data cutoff date : 12OCT2022 Database snapshot date : 25OCT2022) Output File: ./nda2_ub1044/C4591044_1MPD_C2/adae_091_c2_1m

Many of the AEs were consistent with reactogenicity events that were reported as AEs (eg, fatigue, injection site pain or erythema, chills, headache, myalgia), and included lymphadenopathy which is recognized as a potentially vaccine-related event. Each non-reactogenicity type event was reported in no more than 2 participants, of which only 1 event (menstruation irregular) was considered by the investigator to be possibly related to study intervention as summarized below.

- One event of menstruation irregular (missed menstrual period) was reported in a female participant between 20 and 30 years of age, considered by the investigator as related to study intervention. AE onset was 10 days after vaccination and resolved 25 days after onset. No further details were specified.

Immediate Adverse Events

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

Related Adverse Events

AEs assessed as related by the investigator were reported by 12 participants, and all but 1 (menstruation irregular, discussed above) were consistent with reactogenicity events that were reported as AEs. Most related AEs were in the SOC of general disorders and administration site conditions, reported by 6 participants. Additionally, lymphadenopathy was reported by 2 participants in the 18 to 55 years of age group: 1 received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg and the other received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60-µg.

Deaths and Serious Adverse Events
One SAE of dyspnoea (shortness of breath) was reported in a participant in the >55 years of age group who received a booster dose of BNT162b2 bivalent 30-µg. This SAE was reported in a participant between 70 and 80 years of age, considered by the investigator to be severe and not related to study intervention. AE onset was 15 days after vaccination and was ongoing as of the data cutoff date (12 October 2022). No further details were specified.
No deaths were reported from study vaccination through 1 month post vaccination.

Adverse Events Leading to Withdrawal
There were no discontinuations due to AEs from study vaccination through 1 month post vaccination.

Other Significant Adverse Events

No AEs of anaphylaxis/hypersensitivity, appendicitis, Bell's palsy, myo/pericarditis were reported up to 1 month post vaccination. Two cases of lymphadenopathy were reported from study vaccination up to 1 month post vaccination as summarized below:

- One case was in a participant between 40 and 50 years of age with onset 2 days post vaccination, of left axillary lymphadenopathy considered by the investigator as related to study intervention, and it was reported as resolved within 6 days after onset.

- The other case was in a participant between 50 and 60 years of age with onset 2 days post vaccination, presenting with left axillary lymph node swelling. It was considered by the investigator as related to study intervention, and it was reported as resolved within 8 days after onset.

Safety in special populations

Geriatric Use
Clinical studies of BNT162b2 Bivalent (Original/Omicron BA.4-5) include participants ≥65 years of age whose data contribute to overall assessment of safety and efficacy. The clinical data from older adults (>55 years of age) have demonstrated a predominantly mild reactogenicity profile, and a lower frequency of reactions/systemic events compared with younger adults.

Paediatric Use
Clinical paediatric studies of BNT162b2 Bivalent (Original/Omicron BA.4-5) includes participants 6 months to <12 years of age enrolled in the ongoing study C4591048. The clinical data available so far have shown a predominantly mild reactogenicity profile in this age group.

Use During Pregnancy and Lactation
Individuals who were pregnant or breastfeeding were not eligible to participate in Study C4591044 and Study C4591048 Substudy D. No pregnancies have been reported in Study C4591044 and Study C4591048 Substudy D as of the respective data cut-off dates. No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy.

Use in Immunocompromised Individuals
Individuals who are immunocompromised or taking immunosuppressive therapy at the time of vaccine administration may have diminished response to immunization. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination, were not eligible to participate in Study C4591044 and Study C4591048. There are limited data on the safety and effectiveness of the BNT162b2 Bivalent (Original/Omicron BA.4-5) in this patient population at the time of this submission.

Post marketing experience

Limited post authorization safety data for BNT162b2 Bivalent (Original/Omicron BA.4-5) are currently available (post-authorization safety data for BNT162b2 Bivalent [Original/Omicron BA.4-5] in individuals 5 years of age and older was previously submitted). Based on available clinical study data, the safety profile for Omicron-modified vaccine is expected to be similar to the safety profile of BNT162b2. The MAH will continue to monitor all emerging post authorization safety data for BNT162b2 Bivalent (Original/Omicron BA.4-5) for pharmacovigilance and risk management purposes.

MAH Conclusions

Given the antigenic differences in currently circulating strains of SARS-CoV-2 compared to the original wild-type strain, uncertainties in the evolution of SARS-CoV-2 and the genetic and antigenic characteristics of future variants, an updated vaccine composition that contains both index virus and Omicron (the most antigenically distinct SARS-CoV-2 VOC to date) may provide a broader antibody response against circulating and emerging variants, while retaining cross-reactive immunity and cross-protection from severe illness caused by other VOCs.

Overall, in paediatric clinical study participants from Study C4591048 Substudy D (Group 2), the reactogenicity profile within 7 days after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) vaccine was generally similar in severity, with lower frequencies reported, compared to those previously observed in association with primary and booster (third) doses of the original BNT162b2 vaccine within the respective age groups. Overall, in clinical study participants ≥12 years of age from Study C4591044 (Cohort 2 and Cohort 2 [Groups 2 and 4] and Cohort 3 combined), the reactogenicity profile within 7 days after BNT162b2 bivalent (Original/Omicron BA.4-5) was generally similar to that previously observed in association with booster doses of an Omicron BA.1-modified BNT162b2 bivalent vaccine and to the original BNT162b2 vaccine within the respective age groups. Analysis of immunogenicity data from C4591044 Cohort 2 (≥12 years of age) and Cohort 2 (Groups 2 & 4) & Cohort 3 (Groups 1 & 2) combined (≥18 years of age) for BNT162b2-experienced participants who received a booster (fourth dose) with BNT162b2 Bivalent (Original/Omicron BA.4-5) 30 or 60 µg demonstrated a robust immune response against Omicron BA.4/BA.5. Superiority and noninferior statistical hypothesis testing of BNT162b2 Bivalent (Original/Omicron BA.4-5) compared with BNT162b2 30 µg suggest that BNT162b2 Bivalent (Original/Omicron BA.4-5) will provide improved clinical benefit against COVID-19, particularly with respect to the immune response elicited against Omicron BA.4/BA.5.

Real-world data have shown that after vaccination with BNT162b2, in the presence of the now-predominant Omicron variant, vaccine effectiveness against symptomatic COVID-19 is lower and wanes more quickly compared to prior variants. In time periods predominated by BA.4/BA.5 sublineages, real-world studies indicate that 2 or 3 doses of monovalent mRNA vaccines may offer significantly reduced levels and duration of protection against COVID-19 outcomes, including severe endpoints like hospitalization, and less severe endpoints such as emergency department visits, urgent care, and outpatient visits, compared to protection against prior variants and sublineages. A bivalent Omicron variant-modified vaccine addresses this urgent unmet need to improve vaccine protection against Omicron BA.4/BA.5 and future variants, with previously demonstrated broad protection against the original (WT) SARS-CoV-2 strain and prior variants (until emergence of Omicron), now with addition of specificity for Omicron BA.4/BA.5. Primary vaccination with the bivalent vaccine formulation is expected to elicit a broad immune response in individuals who have not yet been exposed to, or vaccinated against, SARS-CoV-2. This expectation is supported by clinical data as well as recent real-world studies from the US, Israel, Nordic countries (ie, Denmark, Finland, Norway, and Sweden), and the UK describing bivalent vaccine protection against currently circulating Omicron sublineages. These

studies show that vaccination with bivalent mRNA booster vaccines is associated with increased protection against symptomatic and severe illness, with higher effectiveness seen against more severe outcomes such as hospitalization, relative to (original) monovalent-only mRNA vaccination among individuals ≥ 5 years of age, including those 5 to 11 years of age, and ≥12 years of age. Two of these studies (one published and one preprint), both conducted in the US, reported that bivalent boosters were more effective than monovalent boosters among individuals 5 to 11 years, and 12 years and older, during periods in which recent Omicron sublineages, including BA.5, BQ.1/BQ.1.1, and XBB/XBB1.5, were prevalent. In addition, at the VRBPAC held on 26 January 2023, the CDC reported that relative effectiveness of bivalent mRNA boosters against symptomatic illness among adults ≥18 years of age was similar for BA.5-related and XBB/XBB.1.5-related COVID-19.

Implementation of a dosing regimen that uses the bivalent vaccine formulation for primary vaccination is anticipated to provide both clinical and practical benefits. Primary vaccination with bivalent vaccines is expected to elicit a broad immune response in individuals who have not yet been exposed to, or vaccinated against, SARS-CoV-2. From the practical perspective, in the current landscape where multiple vaccine formulations are in use, moving to a single vaccine formulation for COVID-19 immunization reduces operational complexity as practitioners and pharmacies no longer need to stock multiple formulations, and may reduce vaccine administration errors due to the complexity of the number of different vial presentations. Reduced complexity is expected to facilitate clearer communication, which could lead to improved vaccine uptake and compliance.

In summary, the available clinical data from the COVID-19 vaccine program collectively support approval of a 2-dose primary series with BNT162b2 Bivalent (Original/Omicron BA.4-5) at the 10 µg or 30 µg dose level in children 5 to 11 years of age (10 µg) and in adolescents/adults ≥12 years of age (30 µg), which is reasonably anticipated to have a similar safety profile (ie, reactogenicity and AEs) and similar or better effectiveness (ie, antigen specific neutralizing antibody response) in the current epidemiologic setting compared to the approved original BNT162b2 vaccine.

2.5.1. Discussion on clinical safety

With the aim to support the use of the bivalent COVID-19 Original/Omicron BA.4-5 vaccine administered as a primary series at 10µg (5+5µg) for subjects aged ≥5 to <12 years and at 30µg (15+15 µg) in subjects ≥12 years of age, data from two studies (C4591048 substudy D and C4591044) have been presented where these vaccines have been administered as a booster dose to each age group. The studies are described separately below. No data has been provided where the bivalent vaccine has been used as primary series.

BNT162b2 bivalent Original/Omicron BA.4-5 at 5+5 µg in subjects aged ≥5 to <12 years

Study C4591048 Substudy D (group 2) is an open-label study to evaluate the safety, tolerability and immunogenicity of a fourth dose of the bivalent BNT162b2 (Original/Omicron BA.4-5) at 5+5 µg in participants ≥5 to <12 years of age who have received 3 prior doses of BNT162b2 Original at 10 µg. Data cut-off was 25 November 2022. Up to the cut-off date, 113 subjects aged ≥5 to <12 years received the bivalent vaccine as a fourth dose. Median time between dose 3 (of BNT162b2 Original 10µg) and dose 4 was 154 days and median time for follow-up was 1.6 months.

Reactogenicity: Pain at injection site (64%) was the most frequent reported local reaction, followed by redness (7%) and swelling (5%) when the bivalent Original/Omicron BA.4-5 at 5+5µg was administered as a fourth dose. The majority of the reactions were mild to moderate in severity, no grade 4 reaction was reported. Fatigue (41%) was the most commonly reported systemic event followed by headache (25%) and muscle pain (14%) when the bivalent Original/Omicron BA.4-5 at

5+5µg was administered as a fourth dose. Fever was noted in 5% of the subjects of which two of them reported a body temperature >38.9°C to 40°C, but none of them reported a body temperature >40°C. Antipyretic or pain medication use was reported by 23% of the participants.

BNT162b2 Original at 10µg administered as a third dose (booster dose) to subjects aged ≥5 to <12 years was evaluated in EMEA/H/C/005735/II/0129 procedure where 400 subjects received dose 3. That evaluation also included a comparison of the safety results between the previously administered primary series and the third dose in the same study population (study C4591007). In this study, pain at injection site (74%) was the most commonly reported local reaction after dose 3 (78% dose 1; 72% dose 2). Fatigue (46%), followed by headache (34%) was the most commonly reported systemic reaction after dose 3. In general, the safety results obtained after dose 3 were in line with what had been seen after the primary series. It was however noted that antipyretic pain medication was used by 31% after dose 3, which was a higher frequency compared to dose 2 (22%) and dose 1 (13%). The frequency of fever was not higher after dose 3 (9% dose 2; 7% dose 3), but a slightly increase of reported headache (30% dose 2; 34% dose 3) and muscle pain (13% dose 2; 18% dose 3) could be an explanation for the higher use of antipyretic pain medication after dose 3.

Taken together, in this limited study population of 113 subjects, the frequency and severity of reported local reactions and systemic events appears to be in line with what has previously been seen in another study where primary series as well as a third dose were evaluated.

Up to the cut-off date, AEs were reported in four (3.5%) subjects. One subject reported an AE which was considered related to vaccination (lymph node palpable), one subject reported a severe AE (flu infection) and the other two reported AEs were otitis media and sore throat. No immediate AEs, SAEs, or AEs leading to withdrawal were reported up to the cut-off date. Lymphadenopathy is already included in the product information of the vaccine. No new safety concern was detected in this population of 113 subjects.

BNT162b2 bivalent Original/Omicron BA.4-5 at 15+15 µg in subjects ≥12 years of age

This study was previously evaluated in EMEA/H/C/005735/X/0147 procedure with a cut-off date 12 Sept 2022 and in EMEA/H/C/005735/MEA/059.1 procedure with similar cut-off date (12 Oct 2022) as in this application.

Study C4591044 Cohort 2 included 528 subjects aged ≥12 years who received a fourth dose of bivalent BNT162b2 Original/Omicron BA.4-5 at either 30µg (12-17 years) or at either 30µg/60µg (≥18 years). All subjects except one had a duration of follow up of ≥ 1 month <2 months after study vaccination.

Reactogenicity: The most reported local reaction was pain at the injection site (56-94%), with the highest frequency (94%) reported in the group 18-55 years of age that received the bivalent vaccine 60 µg, in this group was also reported one event of severe redness. One severe event of pain at the injection site was reported among subjects aged 12-17 years that received the bivalent vaccine 30 µg. Except for those severe events, the reported local reactions were mild to moderate in severity. Among the adult subjects, a slightly higher frequency of moderate events was reported among the subjects that received 60 µg compared to 30 µg. Fatigue was the most commonly reported systemic event (39-76%), followed by headache (30-50%), muscle pain (20-42%) and chills (12-27%). The lowest frequency was reported among the subjects aged >55 years that received 30 µg. Most of the events were mild to moderate in severity. Fever was reported in 5-14% of the subjects, the highest frequency was reported among subjects aged >55 years that received 60 µg. Severe events of fever (i.e., >38.9 to 40°C) were reported in one subject in the age group 12-17 years; two subjects in the age group 18-<55 60 µg and two subjects in the age group >55 years 60 µg.

Overall, the reactogenicity data from subjects >12 years of age included in this cohort where only the bivalent Original/Omicron BA.4-5 vaccine was administered at doses of 30 or 60 µg, supports the trend noted earlier among subjects receiving 30 vs 60 µg as original or bivalent formulations: a higher dose results in a higher frequency and a slightly higher severity of reactogenicity events. Furthermore, older subjects report lower frequency of local and systemic events compared to younger subjects.

Any AE was reported in 3-8% of the age groups, most of the events were related to reactogenicity. There were no events of death reported and no discontinuations due to AEs from study vaccination up to one month after vaccination. One SAE of dyspnoea was reported 15 days after vaccination in a participant between the age of 70 and 80 who received the bivalent 30 µg vaccine. Because of the TTO of 15 days, it can be agreed with the investigator that the event was not considered related to the vaccine.

No events of anaphylaxis/hypersensitivity, appendicitis, Bell's palsy, myo/pericarditis were reported up to 1 month post vaccination. Two events of lymphadenopathy were reported, however lymphadenopathy is already listed as an adverse reaction in section 4.8 of the SmPC. No new safety concern was identified in this study population.

2.5.2. Conclusions on clinical safety

Two studies have been presented where the bivalent BNT162b2 Original/Omicron BA.4-5 vaccine has been administered as a fourth dose. One study included 113 participants aged ≥5 to <12 years that received a dose of 5+5 µg and the other study where the fourth dose was administered at 15+15 µg to subjects aged ≥12-17 years and at 15+15µg or 30+30 µg to subjects ≥18 years of age (n=528). Among the subjects that received either 30 or 60 µg, a clear trend to higher reactogenicity with higher dose was noted. The frequency of local and systemic events was overall in line with what was previously reported in studies where the BNT162b2 original 30 µg was administered as primary series or third dose.

From a safety perspective, this suggests that the bivalent vaccine could be used as a primary series at the proposed dose of 15+15µg in subjects aged ≥12 years of age.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

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

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

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

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

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

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

2.6.1. Safety Specifications

Table SVIII.1: Summary of the Safety Concerns

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

Discussion on safety specification

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

Conclusions on the safety specification

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

2.6.2. Pharmacovigilance plan

Routine pharmacovigilance

The changes related to the formulation under assessment in procedure X176 have been assessed in the corresponding line extension procedure and found acceptable.

Summary of planned additional PhV activities from RMP

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

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

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

The two newly added Non-interventional studies are:

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

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

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

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

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	myocarditis and pericarditis, in individuals of any age who received the Pfizer-BioNTech COVID-19 bivalent Omicron-modified Vaccine since its availability under an EUA using electronic health records and claims data from data partners participating in the Sentinel System.			
C4591052 (EU)	Post-approval observational studies using real-world data are needed to assess the association between Pfizer-BioNTech COVID-19 bivalent Omicron-modified Vaccine and safety events of interest among persons administered the vaccine in the overall EU population. This observational study will capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the COVID-19 bivalent Omicron-modified	Myocarditis/pericarditis Use in pregnancy AESI-based safety events of interest including vaccine associated enhanced disease Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long term safety		Protocol synopsis: 04 Jan 2023 Protocol: 30 Apr 2023 Final CSR: 31 Oct 2025

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	Vaccine since its availability.			

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

Note that the protocol synopses for these two PASS have already been assessed and accepted previously in separate procedures, *i.e.* EMEA/H/C/005735/MEA/062 [C4591052] and EMEA/H/C/005735/MEA/064 [C4591051]. Assessment of the full study protocols is currently ongoing.

Overall conclusions on the PhV Plan

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

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

2.6.3. Plans for post-authorisation efficacy studies

Not applicable.

2.6.4. Risk minimisation measures

Routine Risk Minimisation Measures

No changes are proposed. This is accepted.

Additional risk minimisation measures

Not applicable.

Overall conclusions on risk minimisation measures

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

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

Part VI Summary of the risk management plan

PRAC concludes that the updates are administrative and acceptable.

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

2.6.5. Conclusion on the RMP

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

2.7. Update of the Product Information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

As a consequence of the update of the ATC code, section 5.1 of the SmPC has been updated.

As a consequence of the simplification of the posology, sections 4.2, 4.4, 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

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

2.7.2. Labelling exemptions

The following exemptions from labelling requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the Questions and Answers on labelling flexibilities for COVID-19 vaccines (EMA/689080/2020 rev.1, from 16 December 2020) document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities.

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

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

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

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

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

2.7.3. Additional monitoring

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

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

2.7.4. Quick Response (QR) code

The updates of the QR code/URL to include further references to Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection and Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection as well as the necessary layout changes on the website shall be submitted and assessed via an Article 61.3 notification (post-authorisation).

3. Benefit-Risk Balance

3.1. Introduction

This application concerns the extension of the indication of the BNT162b2 Bivalent (WT/OMI BA.4/BA.5), currently only indicated as a booster, to a two dose primary series for children 5-11 years of age (10 µg) and adolescents/adults ≥12 years of age (30 µg).

There are no vaccine efficacy data included in the application; the evaluation is solely based on immunogenicity, along with a scientific argumentation of extrapolation. There are no data submitted investigating the bivalent BNT162b2 (Original/Omi BA.4/BA.5) as a primary series in any age group: the evaluation is solely based on extrapolation from booster studies where the product was given as the fourth dose.

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

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

3.2. Therapeutic Context

3.2.1. Disease or condition

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

It is noteworthy that the virology of the disease is still steady changing, with new SARS-CoV-2 variants overtaking previous ones epidemiologically. This has also implications for vaccine prophylaxis as certain variants display evasion against both naturally and vaccine-acquired immunity.

3.2.2. Available therapies and unmet medical need

While care for individuals who have COVID-19 has improved with clinical experience, vaccination is the most effective medical countermeasure to decrease risk of disease.

The majority of the global population has either received COVID-19 vaccination or been exposed to the virus. The need for primary vaccination is considerably smaller than previously, but there is still demand for a vaccine that can be used for primary vaccination. The original Comirnaty is still available, however it may be more appropriate to use variant adapted vaccines also for primary vaccination. There is currently no Omicron vaccine approved for primary vaccination in any age group.

3.2.3. Main clinical studies

Two studies have been presented where the bivalent BNT162b2 Original/Omicron BA.4-5 has been administered as a fourth dose to subjects aged ≥5 to <12 years and ≥12 years of age.

Study C4591048 Substudy D Group 2 (≥5 to <12 Years of Age): Booster (Fourth Dose) with BNT162b2 Bivalent (Original/Omicron BA.4-5) at 10 µg

Substudy D is an open-label study to evaluate the safety, tolerability, and immunogenicity of a fourth dose of the bivalent BNT162b2 (Original/Omi BA.4-5) at 5+5µ in participants ≥5 to <12 years of age who have received 3 prior doses of BNT162b2 Original at 10 µg. Data cut-off was 25 November 2022. Safety data is available for 113 subjects, at the cut-off the median follow-up time for safety after vaccination was 1.6 months.

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

This study was previously evaluated in EMEA/H/C/005735/X/0147 procedure with a cut-off date 12 Sept 2022 and in EMEA/H/C/005735/MEA/059.1 procedure with similar cut-off date (12 Oct 2022) as in this application.

The safety population in this study (cohort 2) included 528 participants ≥12 years of age who received a fourth dose of BNT162b2 bivalent (Original/Omicron BA.4-5) 30- or 60-µg. Median duration of follow-up after vaccination was 1.5 months.

3.3. Favourable effects

A substantial increase in GMT to Omicron BA.4/5 and the reference strain is seen after the bivalent BNT162b2 (Original/Omi BA.4/BA.5) is administered as a booster in all the investigated age groups.

The superiority criterium for BNT162b2 Bivalent (WT/OMI BA.4/BA.5) in neutralization of Omicron BA.4/5 in comparison to the original BNT162b2 in the age group >55 years were met: GMR 2.91 (2-sided 95% CI: 2.45, 3.44). The non-inferiority criterium for the product were also met with regards to the anti-omicron BA.4/5 seroresponse rate in the age group >55 years.

The secondary immunogenicity objective to show noninferiority of the anti–reference-strain immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) relative to the anti–reference-strain immune response elicited by BNT162b2 in the >55-age group was also met. The MAH also showed

non-inferiority in anti-omicron BA.4/5 GMR and seroresponse rate in the 18-55 years of age compared to the >55 years group in participants who received the bivalent vaccine.

Considering that:

- Bivalent Original/Omicron BA.1 has demonstrated superior immune responses to BA.1 and non-inferior responses to the reference strain
- Any bivalent original/variant vaccine is considered to have similar characteristics as the Original/Omicron BA.1 vaccine
- Booster responses of the same magnitude can be extrapolated to primary vaccination
- No primary vaccination data will be available
- It is likely that primary vaccination with a vaccine covering currently circulating strains is superior against these, compared to primary vaccination with the original vaccine
- In the dose-finding study C4591001 for the original formulation, it was shown that 10 µg of mRNA encoding the spike antigen elicited a somewhat comparable response as the 30 µg formulation in healthy adults

The use of a primary vaccination schedule for the bivalent vaccine is deemed to be sufficiently substantiated.

In summary, it is reasonably likely that a primary series with the bivalent BNT162b2 (Original/Omi BA.4/BA.5) will yield a better or comparable immune response as the original formulation against the strains investigated.

3.4. Uncertainties and limitations about favourable effects

There are no submitted data investigating the bivalent BNT162b2 (Original/Omi BA.4/BA.5) as a primary series in any age group.

There are no vaccine efficacy data included in the application; the evaluation is based on immunogenicity.

There is no established serological correlate of protection. Therefore immunobridging to a vaccine regimen known to provide protection is used to estimate efficacy.

The effect is estimated by extrapolation from booster studies, where a single dose of the bivalent vaccine was administered. In the age group 12-17 years there is a lack of an active comparator. Although, in the age group 5-11 years, the bivalent vaccine does not perform substantially better than the original formulation with regards to neutralization of Omicron BA.4/5 or the reference strain, the comparator group was imported from a previous study and thus the comparison is not optimal due to different number of doses received by the participants as well as a continuously changing epidemiology and virology of the disease.

The validity of the comparison of the bivalent Original/Omicron BA.4-5 to the original or Original/Omicron BA.1 was questioned, as it was not clear why the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) performed better with regards to neutralization and seroresponse rate for Omicron BA.1 and the reference strain in comparison to the other two formulations. The MAH explained that linear regression model-based analysis adjusting the baseline neutralising titre level has been used to overcome the problem with incomparable historic control. GMR originates from model based GMT calculation, which is considered as an intermediate estimate in order to reach a more valid and meaningful model-based GMR.

Moreover, it is noteworthy that when the immunogenicity of the bivalent vaccine against new variants in participants >55 years of age (*n* = 36) was investigated, the results were diverse. While a reasonable increase in neutralizing titers were observed against Omicron BA.4.6 1 month post-vaccination, the effect against BQ.1.1, BA.2.75.2 and XBB was very low. Although these *in vitro* analyses do not represent the full immune response elicited *in vivo*, which is likely more potent, it was noted that the neutralization effect against emerged variants is reduced.

3.5. Unfavourable effects

In study **C4591048** Substudy D group 2 where 113 subjects aged **≥5 to <12 years** received BNT162b2 bivalent Original/Omicron BA.4-5 at 5+5 µg as a fourth dose, the reactogenicity appears to be in line with what was previously identified where BNT162b2 Original at 10 µg was administered as primary series and dose 3 (EMEA/H/C/005735/II/0129 procedure). When the bivalent vaccine was administered as a fourth dose, the most commonly reported local reaction was pain at injection site (64%) and the most commonly reported systemic events were fatigue (41%), headache (25%) and muscle pain (14%).

In study **C4591044** that included 528 subjects aged **≥12 years** (cohort 2), a fourth dose of bivalent BNT162b2 Original/Omicron BA.4-5 at either 30µg (12-17 years) or at either 30µg/60µg (≥18 years) was administered to the participants. The most reported local reaction was pain at injection site (56-94%), with the highest frequency (94%) reported in the group 18-55 years of age that received the bivalent vaccine 60 µg. Fatigue was the most commonly reported systemic event (39-76%), followed by headache (30-50%), muscle pain (20-42%) and chills (12-27%). There was a clear trend among subjects receiving 30 vs 60 µg that a higher dose results in a higher frequency and a slightly higher severity of reactogenicity events. Furthermore, older subjects report lower frequency of local and systemic events compared to younger subjects.

3.6. Uncertainties and limitations about unfavourable effects

Safety data for BNT162b2 Original/Omicron BA.4-5 vaccine at 5+5 µg and at 15+15 µg is only available when administered as a fourth dose. None of the age groups has received the bivalent vaccine as a primary series.

3.7. Effects Table

Effects Table for BNT162b2 Original/Omicron BA.4-5 at 30µg

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Immunogenicity against Omicron BA.4-5	4th dose bivalent (5/5) µg to **5-<12y**, after 3 doses original 3 µg	GMT (95% CI) 1m post dose	N= 101 1836.1 (1593.8, 2115.2)	N= 112 1632.5 (1427.5, 1867.0)	Comparator has received numerically less doses (3) than active arm (4). Model based descriptive GMR.	Study C4591048 Substudy D
		GMR	1.12 (0.92, 1.37)			
Immunogenicity against Omicron BA.4-5	4th dose bivalent (15/15) µg to **12-17y**, after 3 doses original 3 µg	GMT (95% CI) 1m post dose	N = 105 Prevax: 1105.8 (835.1, 1464.3) 1 month: 8212.8 (6807.3, 9908.7)	n/a	No comparator	Study C4591044
Immunogenicity against Omicron BA.4-5	4th dose bivalent (15/15) µg to **18-55y**, after 3 doses original 3 µg	GMT (95% CI) 1m post dose	N = 297 Prevax: 569.6 (471.4, 688.2) 1 month: 4455.9 (3851.7, 5154.8)	N = 282 Prevax: 205.4 (170.3, 247.7) 1 month: 938.9 (802.3, 1098.8)	Comparator group that received fourth dose of the original was >55 years	Study C4591044
Immunogenicity against Omicron BA.4-5	4th dose bivalent (15/15) µg to **>55y**, after 3 doses original 3 µg	GMT (95% CI) 1m post dose	N = 284 Prevax: 458.2 (365.2, 574.8) 1 month: 4158.1 (3554.8, 4863.8)	N = 282 Prevax: 205.4 (170.3, 247.7) 1 month: 938.9 (802.3, 1098.8)	(same comparator as above)	Study C4591044
Immunogenicity against Omicron BA.4-5	4th dose bivalent (15/15) µg to **>55**, after 3 doses original 3 µg	GMT (95% CI) 1m post dose	N= 282 3373.4 (3000.3, 3793.0)	N= 273 1160.7 (1030.3, 1307.7)	Active arm and comparator have both received 4 doses	Study C4591044
		GMR	2.91 (2.45, 3.44)		Bivalent/Original among	Superiority met

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					>55	
	4th dose bivalent (15/15) µg to **>55** and **18-55** after 3 doses original 3 µg	GMT (95% CI) 1m post dose	N= 282 4344.4 (3850.2, 4902.1)	N= 294 4254.2 (3779.6, 4788.4)		
		GMR	0.98 (0.83, 1.16)		Bivalent 18-55/ bivalent >55	Non-inferiority met
Unfavourable Effects						
Fatigue	≥5 to <12 years		Dose 4: 41%			Study C4591048 N=113
Headache	≥5 to <12 years		Dose 4: 25%			Study C4591048 N=113
Muscle pain	≥5 to <12 years		Dose 4: 14%			Study C4591048 N=113
Fever	≥5 to <12 years		Dose 4: 5%			Study C4591048 N=113
Pain at the injection site	≥12 years (3 age groups: 12-17; 18-55 and >55 years)		Dose 4 30µg: 56-79% 60µg: 71-94%		Transient events, majority mild to moderate severity. Higher severity among the subjects that received 60 µg	Study C4591044 N=528
Fatigue	≥12 years (3 age groups: 12-17; 18-55 and >55 years)		Dose 4 30µg: 39-67% 60µg: 53-69%			Study C4591044 N=528
Headache	≥12 years (3 age groups: 12-17; 18-55 and >55 years)		Dose 4 30µg: 30-50% 60µg: 36-45%			Study C4591044 N=528
Muscle pain	≥12 years (3 age groups: 12-17; 18-55 and >55 years)		Dose 4 30µg: 20-31% 60µg: 23-42%			Study C4591044 N=528
Fever	≥12 years (3 age groups: 12-17; 18-55 and >55 years)		Dose 4 30µg: 5-9% 60µg: 12-14%			Study C4591044 N=528

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

3.8. Benefit-risk assessment and discussion

3.8.1. Importance of favourable and unfavourable effects

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

Based on the argument of extrapolation outlined above under "favourable effects", it is considered reasonably probable that the variant adapted vaccines are also effective as primary vaccination. The currently submitted data are considered supportive.

The known unfavourable effects at administration of the bivalent BNT162b2 Original/Omicron BA.4-5 at 30 µg to subjects aged ≥12 years are considered acceptable in terms of reactogenicity. There are no new safety concerns based on the study conducted; however the study size did not allow detection of rare adverse events. The overall experience of Comirnaty variant vaccine safety has been previously reviewed. Strain composition has not been associated with any relevant differences in clinical safety. Therefore, safety may be extrapolated to the use of the bivalent vaccine for a primary series.

3.8.2. Balance of benefits and risks

The benefit/risk balance as primary series of the 10 μg formulation for children 5 to 11 years of age, and the 30 μg formulation for adolescents/adults ≥12 years of age, of the Comirnaty Original/Omicron BA.4-5 Vaccine is considered positive.

3.9. Conclusions

The overall B/R of the bivalent BNT162b2 Original/Omicron BA.4-5 is considered positive.

4. Recommendations

Outcome

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

Variations requested		**Type**	**Annexes affected**
A.6	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	Type IA	I
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

C.I.6.a: Extension of indication to include Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose

concentrate for dispersion for injection and Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection for use as primary vaccination course against COVID-19 in children aged 5 to 11 years and in individuals 12 years of age and older, respectively, based on interim results from studies C4591044 and C4591048. Study C4591044 is an interventional, randomized, 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, while study C4591048 is a phase 1/2/3 master study to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b2 RNA-based vaccine candidates in healthy children. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10 of the RMP has also been submitted.
In addition, the MAH took the opportunity to introduce minor editorial changes to the product information.

A.6: Change of the ATC Code of tozinameran, riltozinameran and famtozinameran from J07BX03 to J07BN01.

In addition, the vaccine posology has been simplified for all approved formulations. As a consequence, sections 4.2, 4.4, 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance.

The group of variations leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, IIIA and IIIB and to the Risk Management Plan are recommended.