EMA/CHMP/446369/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/005735/II/0188/G

Invented name: COMIRNATY

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

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

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	29 Aug 2023	29 Aug 2023
☐	CHMP Rapporteur Assessment Report	02 Oct 2023	03 Oct 2023
☐	PRAC Rapporteur Assessment Report	09 Oct 2023	02 Oct 2023
☐	PRAC members comments	13 Oct 2023	13 Oct 2023
☐	CHMP members comments	16 Oct 2023	16 Oct 2023
☐	Updated PRAC Rapporteur Assessment Report	17 Oct 2023	n/a
☐	Updated CHMP Rapporteur Assessment Report	19 Oct 2023	n/a
☐	PRAC endorsed relevant sections of the assessment report	24 Oct 2023	24 Oct 2023
☐	Start of written procedure	24 Oct 2023	24 Oct 2023
☒	Opinion	26 Oct 2023	26 Oct 2023

Table of contents

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 9 August 2023 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	None

Grouped application comprising two type II variations as follows:

C.I.4 – Update of section 4.8 of the SmPC in order to update the safety information based on interim (6 months post-dose 3 in 12-15 years old) and final results from study C4591001, listed as a category 3 study in the RMP. This is a phase 1/2/3, placebo-controlled, randomised, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of COMIRNATY against COVID-19 in healthy individuals.

C.I.11.b - Submission of an updated RMP version 10.1 in order to revise RMP milestones of final study reports of other on-going procedures, including other administrative and editorial changes.

The requested group of variations proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

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

Within this type II variation, the MAH has submitted the final data from the clinical study C4591001, listed as a category 3 study in the RMP. Safety interim data to support a proposed update in section 4.8 in the SmPC for adolescents aged 12-15 years who had received one booster dose of BNT162b2 30µg has also been provided.

Efficacy

Study C4591001 was a phase 1/2/3 multicentre, multinational, randomised, placebo-controlled, observer-blind, dose finding, vaccine candidate-selection, and efficacy study in healthy individuals ≥12 years of age. The study population included more than 40,000 individuals. Participants received 2 doses of Original Comirnaty 30 µg and were followed up for up to 2 years post-dose 2. Originally, the study had an active arm and a placebo arm, but after the approval of the vaccine, the participants in the placebo arm were offered vaccination, resulting in a cross-over arm. The study continued with options to receive booster doses with the Original vaccine (3rd and 4th dose). The participants gave 3-5 blood samples to monitor for seroconversion after possible infection (N-antigen antibody detection).

In the current final report, the MAH presented data from asymptomatic infection surveillance (in population without and with evidence of SARS-CoV-2 prior infection), the incidence of SARS-CoV-2

during entire study period and also an immunogenicity analysis of a third dose of BNT162b2 at a lower dose of 5 or 10 µg administered to smaller population (N= 80) of Phase 2/3 participants.

The asymptomatic infection surveillance was performed using two distinct biomarkers: nucleic acid amplification test (NAAT) in a subpopulation (N=4,000) and N-protein detections in the entire population (N=40,000). The NAAT surveillance included several uncertainties as the time window to detect viral RNA is limited, especially if the infection is asymptomatic. Also, the surveillance for asymptomatic infections did not start immediately after vaccination but started 2.9 months post-dose 2 in the United States (USA) and 5.3 months post-dose 2 in Argentina. There were only 44 asymptomatic cases accrued from 3,921 previously uninfected individuals, showing that asymptomatic cases were rather rare or have been missed. The vaccine efficacy (VE) result based on a such testing gave very wide confidence interval (CI), showing the uncertainty, VE= 37.2% (95% CI -20.0%; 66.7%). Among the small population of previously infected individuals, a high rate of asymptomatic cases were detected (45 out of 210). Despite the low numbers, the data showed better protection against asymptomatic infections for participants who have been infected before vaccination compared to the earlier infected but unvaccinated participants VE = 70.8% (95% CI: 39.7%; 87.1%).

N-protein specific antibodies were stable, long-lasting markers for natural SARS-CoV-2 infection regardless of the virus strain. The entire study population was sampled for blood after at least 1 and 6 months post-dose 2 and tested for the seroconversion to N-protein. This analysis showed that Comirnaty Original 30 µg provided protection against asymptomatic infections after 2 doses during the study period: VE = 52.9% (95% CI: 47.2%; 57.9%). As this biomarker is trustable and the study population was very large, it can be concluded that 2 doses of Original Comirnaty provided protection against asymptomatic infections.

The MAH presented also the final data of incidence of SARS-CoV-2 during entire study period. This result illustrated the VE over the 2 years of pandemic, where different new SARS-CoV-2 strains evolved in a short time window. The complete incidence rate (IR)/1000 person-years (PY) was 104.6 for active arm, 125.7 for placebo arm and 169.1 for placebo cross-over arm. The Original Comirnaty was very effective in the beginning of the pandemic. After the authorisation, the placebo arm was offered vaccination and became a cross-over arm. The active arm was offered more doses as the study continued with booster doses. The cross-over arm also received boosters, but with at a later time point and therefore had received fewer doses than the original active arm every time a new strain appeared. Thus, the results are not easily interpretable but are in agreement with waning protection to new variants.

The MAH also submitted immunogenicity results for a lower booster dose (Dose 3) of Original Comirnaty (5 or 10 µg). Lower booster doses of BNT162b2 substantially increased SARS-CoV-2 neutralising antibody response 1 month after Dose 3. Although there was no contemporaneous 30-µg comparator, the data presented showed that a higher booster dose of Original Comirnaty elicits a higher NA titre (geometric mean fold ratio - GMFR 30-µg = 17; 10-µg= 12; 5-µg= 11 for > 55 yoa). Therefore the usage of 30-µg for booster was considered adequate.

In conclusion, the current results show that 2 doses of Original Comirnaty provided protection against asymptomatic infections, and that also lower doses of Original Comirnaty have boosting effect for adults, but the chosen 30-µg is more immunogenic.

No changes to the section 5.1 in the SmPC were suggested and this was agreed by CHMP.

Safety

Phase 1

In the Phase 1 study, primary series of BNT162b1 (10, 20, 30, 100 µg) and BNT162b2 (10, 20, 30 µg) was administered to subgroups including 24 adult participants in each group (total n=195). Most of these participants then received one booster dose of BNT162b2 (30 µg), and an additional booster dose was administered to about half of the study population. After both booster doses, most of the reported adverse events (AEs) were related to reactogenicity and in line with what has previously been observed for the primary series.

Phase 2/3

Phase 2/3 study C4591001 included a total of 46,406 participants aged ≥12 years, of which 99.8% received the two doses included in the primary series of BNT162b2 30µg. The age ranged from 13-92 years, with a median age of 51 years. A total number of 23,406 participants in the Phase 2/3 study received a first booster dose 6-15 months after Dose 2. The median follow-up time after booster dose was 12,3 months.

From the first booster dose up to one month after the first booster dose of BNT162b2 30 µg, the frequency of any AEs was 17% (n=3,818) among the participants ≥16 years of age, many of them were considered related to study vaccine (15% [n=3,377]) and most of them were reactogenicity events.

One severe event of angioedema which was considered related to the booster dose was reported. The event occurred one day after the booster dose and resolved after two days. Angioedema is already listed as an adverse reaction in the SmPC at the frequency uncommon.

One adolescent participant reported one serious adverse event (SAE) of myocarditis 4 days after he received the booster dose. The event resolved within 101 days. Myocarditis is already listed in sections 4.4 and 4.8 of the SmPC.

Booster dose BA.1

BNT162b2-naïve adult participants (n=330) received a dose of the variant vaccine BNT162b2$_{SA}$ (South Africa B.1.351). Among the BNT162b2-naïve participants that received a dose of BNT162b2$_{SA}$, the reported AES was mostly related to reactogenicity.

Low dose booster dose BNT162b2 at 5 or 10 µg

According to protocol amendment 14 and 15, adult participants that had already received the primary series of BNT162b2 30 µg were randomised to receive one low dose booster of BNT162b2 at 5 µg (n=79) or 10 µg (76). None of the participants that received BNT162b2 5 µg reported fever. There was a tendency to lower reactogenicity with lower dose and lower reactogenicity in participants aged >55 years compared to participants aged 18-54 years.

Additional booster dose, protocol amendment 19

Among the participants (N=467) that received a second booster dose of either BNT162b2 at 5 µg (n=33), 10 µg (n=38), 30 µg (n=182) or BNT162b2$_{SA}$ 30 µg (n=211), a higher frequency of any AEs was noted among the participants that received 30 µg (7-9%) compared with those who received low dose i.e., 5 or 10 µg (0-3%). The most reported events were typical for reactogenicity.

Participants 12-15 years of age

In the Phase 2/3 study that included 825 participants aged 12-15 years, the median age was 14 years. The median follow-up time after first booster dose was 9.5 months and from Dose 2, 18.1 months. The median time from Dose 2 to booster dose was 11.2 months (range 6.3-20.1 months).

After the booster dose up to one month after the vaccination, 18% of the participants reported any AEs. Most of these AEs were reactogenicity events (general disorders and administration site conditions and headache) and were considered related to vaccination. Two events of lymphadenopathy were reported, lymphadenopathy is already listed as an adverse reaction in the SmPC. Two events of immediate AEs were reported: fatigue and injection site pain. Three events of severe pyrexia were reported. From Dose 3 and up to the cut-off date (3 Nov 2022), SAEs were reported by 6 participants (depression/worsening of depression and suicidal ideation/suicidal attempt, pectus excavatum, elbow fracture and skull fracture), none of the events were considered related to vaccination. No participants were withdrawn due to AEs.

The results presented for participants aged 12-15 years supported the proposed update of section 4.8 of the SmPC.

No new safety concerns were detected among the participants that received one or two booster doses of BNT162b2 30µg.

The benefit-risk balance of COMIRNATY, remains positive.

3. Recommendations

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

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	None

Grouped application comprising two type II variations as follows:

C.I.4 – Update of section 4.8 of the SmPC in order to update the safety information based on interim (6 months post-dose 3 in 12-15 years old) and final results from study C4591001, listed as a category 3 study in the RMP. This is a phase 1/2/3, placebo-controlled, randomised, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of COMIRNATY against COVID-19 in healthy individuals.

C.I.11.b – Update of the RMP to version 11.0 in order to revise RMP milestones of final study reports of other on-going procedures, including other administrative and editorial changes.

☒is recommended for approval.

Amendments to the marketing authorisation

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

4. EPAR changes

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

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Comirnaty-H-C-005735-II-188-G'

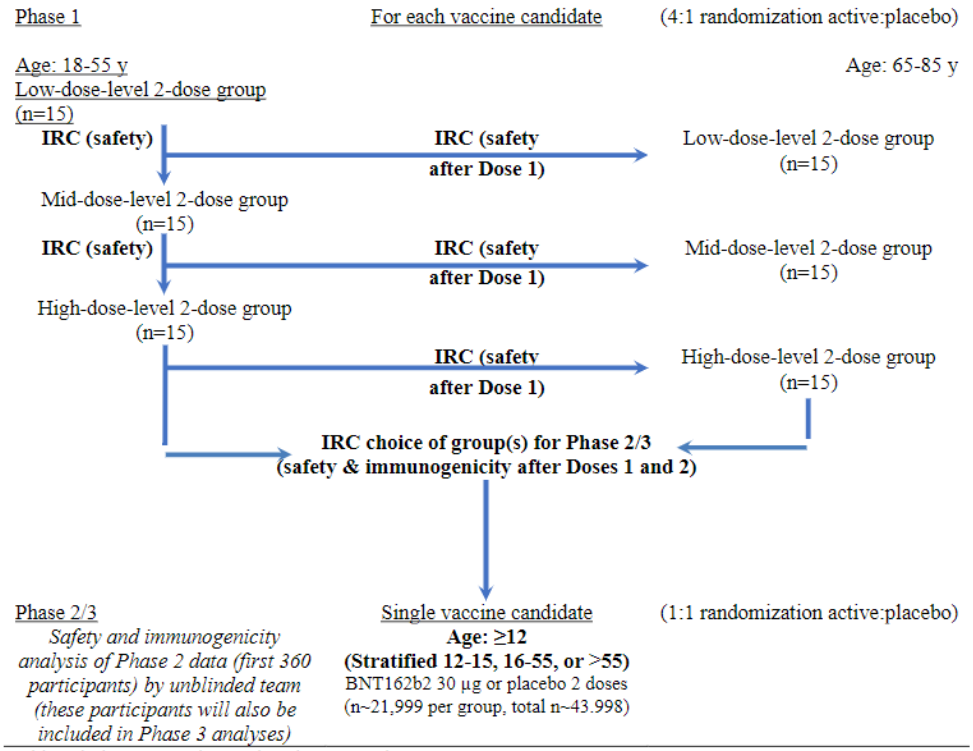
Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

This report includes final data from the clinical study C4591001, listed as a category 3 study in the RMP. Safety interim data to support a proposed update in section 4.8 in the SmPC for adolescents aged 12-15 years has also been provided. No changes to the section 5.1 in the SmPC is suggested.

Study C4591001 is a Phase 1/2/3 multicentre, multinational, randomised, placebo-controlled, observer-blind, dose finding, vaccine candidate-selection, and efficacy study in healthy individuals ≥12 years of age. The study consisted of 2 parts: Phase 1 to identify preferred vaccine candidate(s) and dose level(s) in individuals 18 through 55 and 65 through 85 years of age; and Phase 2/3 as an expanded cohort and efficacy part in individuals ≥12 years of age. These parts and the progression between them, are illustrated in Figure 1 below.

Figure 1: Study C4591001 schema



Abbreviation: IRC = internal review committee.
Source: Module 5.3.5.1 C4591001 Final CSR Appendix 16.1.1, Protocol Section 1.2
Note: Participants who originally received placebo were offered the opportunity to receive BNT162b2 at defined points as part of the study.

Unblinding Considerations

The study was unblinded in stages once all ongoing participants either had been individually unblinded or had concluded their 6-month post–Dose 2 study visit, in the following sequence:

- Phase 1 (after Visit 8 [6-month post–Dose 2 visit]).
- Phase 2/3, ≥16 years of age (after Visit 4 [6-month post–Dose 2 visit]).
- Phase 3, 12 through 15 years of age (after Visit 4 [6-month post–Dose 2 visit]).
- Original Phase 3 participants rerandomised to assess boostability and protection against emerging VOCs (after Visit 306).

Scheduled Visits

Table 1: Scheduled visits

Visit Number	1	2	3	4	5	6	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit[a]**	**Potential COVID-19 Illness Visit[b]**
Visit Window (Days)	**Day 1[c]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**
					ONLY FOR THOSE PARTICIPANTS ORIGINALLY ASSIGNED TO BNT162b2 OR PLACEBO RECIPIENTS WHO DECLINE BNT162b2		
Obtain informed consent	X						
Assign participant number	X						
Obtain demography and medical history data	X						
Perform clinical assessment[d]	X						
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X	
Measure height and weight	X						
Measure temperature (body)	X	X					
Perform urine pregnancy test (if appropriate)	X	X					
Confirm use of contraceptives (if appropriate)	X	X	X				
Collect nonstudy vaccine information	X	X	X	X			
Collect prohibited medication use		X	X	X	X	X	X
Confirm eligibility	X	X					
Review temporary delay criteria	X	X					
Collect blood sample for immunogenicity assessment[e]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	
Obtain nasal (midturbinate) swab	X	X					X
Obtain randomization number and study intervention allocation	X						
Administer study intervention	X	X					
Assess acute reactions for at least 30 minutes after study intervention administration	X	X					
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X						
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X					
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[f]	◄►	◄►					
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[f]		X	X				
Collect AEs and SAEs as appropriate	X	X	X	X[g]	X[g]	X[g]	X
According to eligibility, ascertain willingness to receive BNT162b2 if originally received placebo; if willing, unblind the participant's study intervention assignment (if not already done), and move placebo recipients to the SoA in Section 1.3.3			X ◄►	X			
Collect e-diary or assist the participant to delete application						X[h]	
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to reaching this time point.
b. The COVID-19 illness visit may be conducted as an in-person or telehealth visit. This visit should not be performed if protocol amendment 20 is approved and participants are informed of early study completion prior to potential COVID-19 illness onset.
c. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
d. Including, if indicated, a physical examination.
e. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
f. Reactogenicity subset participants only.
g. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).
h. If protocol amendment 20 is approved and participants are informed of early study completion, e-diary device return should be arranged by the site.

6. Clinical Efficacy aspects

This AR includes summaries of the following Phase 2/3 analyses of Study C4591001:

- Efficacy analysis of BNT162b2 30 µg against asymptomatic SARS-CoV-2 infection in participants without evidence of SARS-CoV-2 infection and in participants with evidence of SARS-CoV-2 infection up to the start of the asymptomatic surveillance period.
- Efficacy analysis of BNT162b2 30 µg against non-S-seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19.
- Incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomisation or subsequently.
- Immunogenicity analysis of a third dose of BNT162b2 at a lower dose of 5 or 10 µg administered to Phase 2/3 participants.

6.1. Methods – analysis of data submitted

Objectives	**Estimands**	**Endpoints**
To evaluate the efficacy of prophylactic BNT162b2 against non-S seroconversion to SARS-CoV-2 in participants without evidence of infection or confirmed COVID-19	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion in participants with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To evaluate the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants without evidence of infection up to the start of the asymptomatic surveillance period	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with no serological or virological evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomisation or subsequently	In participants after receipt of each dose of BNT162b2: Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To describe the efficacy of prophylactic BNT162b2 against asymptomatic SARS-CoV-2 infection in participants with evidence of infection up to the	In participants complying with the key protocol criteria (evaluable participants): 100 × (1 – IRR) [ratio of active vaccine to placebo]	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on central laboratory–confirmed NAAT in participants with serological or virological evidence (up to the

start of the asymptomatic surveillance period		start of the asymptomatic surveillance period) of past SARS-CoV-2 infection
To describe the immune response to a third dose of BNT162b2 (at 30 µg or a lower dose of 5 µg or 10 µg) or a third or fourth dose of $BNT162b2_{SA}$	• GMTs at Dose 3 and subsequent time points • GMFRs from Dose 3 to subsequent time points	SARS-CoV-2 reference strain NTs Data for BNT162b2 at lower dose of 5 or 10 µg are reported in this final CSR.

Efficacy Against Asymptomatic SARS-CoV-2 Infection

VE against asymptomatic SARS-CoV-2 infection was evaluated in 2 ways: through impact on Nucleic Acid Amplification Test (NAAT)-confirmed SARS-CoV-2 infection and impact on seroconversion of N-binding antibody in originally enrolled Phase 2/3 participants not suffering from COVID-19. Data from participants who receive more than 2 doses of BNT162b2 were not included after they receive a third dose.

The incidence of asymptomatic SARS-CoV-2 infection in participants per 1000 person-years based on N-binding antibody seroconversion and central laboratory-confirmed NAAT was assessed to evaluate the asymptomatic efficacy of BNT162b2. In addition, the incidence of confirmed COVID-19 per 1000 person-years of follow-up through the entire study follow-up period was assessed for participants who received BNT162b2 at initial randomisation or subsequently. The assessments included a nasal (midturbinate) swab, which was tested at a central laboratory using an RT-PCR test, or other equivalent nucleic acid amplification– based test (i.e., NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests were assessed. The central laboratory NAAT result was used for the case definition, unless no result was available from the central laboratory, in which case a local NAAT result could be used in the COVID-19 case definition.

Asymptomatic Efficacy and Incidence of Confirmed COVID-19

NAAT-Confirmed SARS-CoV-2 Infection

For participants who consented to participate in an intensive period of surveillance, nasal swabs were obtained to assess SARS-CoV-2 infection by NAAT.

An asymptomatic case of NAAT-confirmed SARS-CoV-2 infection was defined as a positive NAAT result on a nasal swab collected during the surveillance period from participants without COVID-19 symptoms at the time the nasal swab was taken, or within 14 days after it. The onset date of the asymptomatic case is the collection date of the first nasal swab that tested positive.

Seroconversion of N-Binding Antibody

Blood samples for assessment of N-binding antibodies were drawn at multiple scheduled visits. An asymptomatic case of SARS-CoV-2 infection based on seroconversion of N-binding antibody was defined as positive N-binding antibody at a post–Dose 2 visit in participants without serological evidence of infection (determined by negative N-binding antibody) at Visit 1 or virological evidence of infection (determined by negative NAAT result at Visit 1 and Visit 2, and at the time of a potential COVID-19 illness). The requirement for a negative NAAT result at Visit 2 was to focus on assessment of protection against asymptomatic infection after 2 doses of vaccine, to the extent possible in an analysis based on
seroconversion of N-binding antibody, recognizing that it was not possible to identify and exclude all asymptomatic infections that occur after Dose 1 and prior to Dose 2.

A secondary definition will be applied without the requirement for a negative NAAT result at Visit 2 to allow assessment of protection after 1 dose of vaccine. A positive N-binding antibody at a postvaccination visit in participants with negative N-binding antibody at Visit 1 and negative NAAT results at Visit 1 and at the time of a potential COVID-19 illness is considered an asymptomatic case.

6.2. Results

6.2.1. Efficacy

Vaccine Efficacy Against Asymptomatic SARS-CoV-2 Infection

Asymptomatic SARS-CoV-2 Infection Based on Central Laboratory–Confirmed NAAT Result During the Asymptomatic Surveillance Period

Efficacy Populations

In total, 4361 participants participated in the asymptomatic SARS-CoV-2 infection surveillance period with the proportions of participants included in the efficacy populations similar in both vaccine groups. For participants who were excluded from the evaluable efficacy population, the most common reason was because participants did not receive all vaccinations as randomised or did not receive Dose 2 within the predefined window (19 to 42 days after Dose 1). Among the 4258 participants included in the evaluable efficacy population, 3921 participants (89.9%) had no evidence of infection prior to the start of the asymptomatic SARS-CoV-2 infection surveillance period.

Table 2: Efficacy Populations – Asymptomatic SARS-CoV-2 Infection Based on Central Laboratory–Confirmed NAAT Result During the Asymptomatic Surveillance Period

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Participated in asymptomatic SARS-CoV-2 infection surveillance[b]	2280 (100.0)	2081 (100.0)	4361 (100.0)
Dose 1 all-available efficacy population – asymptomatic surveillance	2280 (100.0)	2081 (100.0)	4361 (100.0)
Subjects without evidence of infection prior to the start of asymptomatic surveillance period[c]	2130 (93.4)	1871 (89.9)	4001 (91.7)
Subjects with evidence of infection prior to the start of asymptomatic surveillance period	83 (3.6)	144 (6.9)	227 (5.2)
Subjects excluded from Dose 1 all-available efficacy population – asymptomatic surveillance	0	0	0
Reason for exclusion[d]			
Did not receive at least 1 vaccination	0	0	0
Dose 2 all-available efficacy population – asymptomatic surveillance	2278 (99.9)	2074 (99.7)	4352 (99.8)
Subjects without evidence of infection prior to the start of asymptomatic surveillance period[c]	2130 (93.4)	1871 (89.9)	4001 (91.7)
Subjects with evidence of infection prior to the start of asymptomatic surveillance period	83 (3.6)	139 (6.7)	222 (5.1)
Subjects excluded from Dose 2 all-available efficacy population – asymptomatic surveillance	2 (0.1)	7 (0.3)	9 (0.2)
Reason for exclusion[d]			
Did not receive 2 vaccinations	2 (0.1)	7 (0.3)	9 (0.2)
Evaluable efficacy (asymptomatic surveillance) population	2234 (98.0)	2024 (97.3)	4258 (97.6)
Subjects without evidence of infection prior to the start of asymptomatic surveillance period[c]	2092 (91.8)	1829 (87.9)	3921 (89.9)
Subjects with evidence of infection prior to the start of asymptomatic surveillance period	80 (3.5)	133 (6.4)	213 (4.9)
Subjects excluded from evaluable efficacy (asymptomatic surveillance) population	46 (2.0)	57 (2.7)	103 (2.4)
Reason for exclusion[d]			
Randomized but did not meet all eligibility criteria	0	1 (0.0)	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	43 (1.9)	50 (2.4)	93 (2.1)
Did not consent to participate in the asymptomatic surveillance	0	0	0
Had other important protocol deviations prior to the start of asymptomatic surveillance period	4 (0.2)	7 (0.3)	11 (0.3)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Subjects who had no serological or virological evidence of past SARS-CoV-2 infection (i.e, negative N-binding antibody [serum] result at Visits 1 and 201, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visits) prior to the start of the asymptomatic surveillance period were included in the analysis.
d. Subjects may have been excluded for more than 1 reason.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 18JUL2023 (22:33)
(Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_ASYMP_CSR/adsl_eff_pop_as_nat

The study population for NAAT surveillance was from Argentina and USA. Only about 3% were older than 65.

Table 3: Demographic Characteristics – Subjects Without Evidence of Infection Prior to the Start of the Asymptomatic Surveillance Period – Evaluable Efficacy (Asymptomatic Surveillance) Population

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=2092) n[b] (%)	Placebo (N[a]=1829) n[b] (%)	Total (N[a]=3921) n[b] (%)
Sex			
Male	1118 (53.4)	978 (53.5)	2096 (53.5)
Female	974 (46.6)	851 (46.5)	1825 (46.5)
Race			
White	1926 (92.1)	1666 (91.1)	3592 (91.6)
Black or African American	69 (3.3)	66 (3.6)	135 (3.4)
American Indian or Alaska Native	10 (0.5)	2 (0.1)	12 (0.3)
Asian	57 (2.7)	60 (3.3)	117 (3.0)
Native Hawaiian or other Pacific Islander	2 (0.1)	0	2 (0.1)
Multiracial	22 (1.1)	25 (1.4)	47 (1.2)
Not reported	6 (0.3)	10 (0.5)	16 (0.4)
All others[c]	97 (4.6)	97 (5.3)	194 (4.9)
Ethnicity			
Hispanic/Latino	1102 (52.7)	1053 (57.6)	2155 (55.0)
Non-Hispanic/non-Latino	988 (47.2)	774 (42.3)	1762 (44.9)
Not reported	2 (0.1)	2 (0.1)	4 (0.1)
Country			
Argentina	912 (43.6)	916 (50.1)	1828 (46.6)
USA	1180 (56.4)	913 (49.9)	2093 (53.4)
Age group (years)			
12 to 15	717 (34.3)	658 (36.0)	1375 (35.1)
16 to 55	1140 (54.5)	991 (54.2)	2131 (54.3)
>55	235 (11.2)	180 (9.8)	415 (10.6)
≥65	52 (2.5)	2 (0.1)	54 (1.4)
16 to 17	53 (2.5)	35 (1.9)	88 (2.2)
16 to 25	223 (10.7)	173 (9.5)	396 (10.1)
16 to 64	1323 (63.2)	1169 (63.9)	2492 (63.6)
18 to 64	1270 (60.7)	1134 (62.0)	2404 (61.3)
55 to 64	216 (10.3)	205 (11.2)	421 (10.7)
65 to 74	43 (2.1)	2 (0.1)	45 (1.1)
≥75	9 (0.4)	0	9 (0.2)
75 to 85	9 (0.4)	0	9 (0.2)
Age at vaccination (years)			
Mean (SD)	32.0 (17.42)	31.2 (16.65)	31.6 (17.07)
Median	30.0	30.0	30.0
Min, max	(12, 82)	(12, 72)	(12, 82)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence of past SARS-CoV-2 infection (i.e, negative N-binding antibody [serum] result at Visits 1 and 201, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visits) prior to the start of the asymptomatic surveillance period were included in the analysis.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 22JUN2023 (10:57)
(Cutoff Date: , Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_ASYMP_CSR/adsl_demo_as_nat_wo_eval_eff

Vaccine Efficacy in Participants Without Evidence of SARS-CoV-2 Infection

For the secondary efficacy endpoint, VE for BNT162b2 30 µg (2-dose primary series) against asymptomatic SARS-CoV-2 infection was evaluated in participants without evidence of infection up to the start of the asymptomatic surveillance period (January 2021). Note that the median time between Dose 2 and the start of the asymptomatic surveillance period was 2.9 months for participants in the United States and 5.3 months for participants in Argentina. Cases were counted from the start of the asymptomatic surveillance period.

Among participants included in the evaluable efficacy (asymptomatic surveillance) population, 3921 participants (2092 in BNT162b2 group and 1829 in placebo group) did not have evidence of infection with SARS-CoV-2 prior to the start of the asymptomatic surveillance period. There were 24 asymptomatic SARS-CoV-2 infections in the BNT162b2 (30 µg) group compared to 20 infections reported in the placebo group. The estimated VE was 37.2% (2-sided 95% CI: -20.0%, 66.7%). This descriptive analysis was limited by the accrual of only 44 cases total, resulting in a wide 2-sided 95% CI and limiting the precision of this estimate.

VE against asymptomatic SARS-CoV-2 infection was 40.4% (2-sided 95% CI: -10.8%, 67.8%) for Dose 2 all-available efficacy population.

Table 4: Vaccine Efficacy – Asymptomatic SARS-CoV-2 Infection Based on Central Laboratory–Confirmed NAAT Result – Subjects Without Evidence of Infection Prior to the Start of the Asymptomatic Surveillance Period – Evaluable Efficacy (Asymptomatic Surveillance) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=2092)		Placebo (N[a]=1829)			
Efficacy Endpoint	n[b]	Surveillance Time[c]	n[b]	Surveillance Time[c]	VE (%)	(95% CI[d])
Asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT result during asymptomatic surveillance period	24	0.383	20	0.200	37.2	(-20.0, 66.7)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence of past SARS-CoV-2 infection (i.e, negative N-binding antibody [serum] result at Visits 1 and 201, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visits) prior to the start of the asymptomatic surveillance period were included in the analysis.
a. N = number of subjects in the specified group.
b. n = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group. Time period for case accrual is from the start of the asymptomatic surveillance period to the end of the surveillance period.
d. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adc19nat Table Generation: 18JUL2023 (22:33)
(Snapshot Date: 28APR2023) Output File: ./nda2 unblinded/C4591001 ASYMP CSR/adc19nat ve as nat wo pd2 eval

Assessor´s comment: in comparison to the entire study population, the NAAT tested population was about 10 times smaller. The time window to detect viral DNA is limited, especially if the infection is asymptomatic. Also, the surveillance for asymptomatic infections did not start immediately after the vaccination. The median time between Dose 2 and the start of the asymptomatic surveillance period was 2.9 months for participants in the United States and 5.3 months for participants in Argentina. Cases were counted from the start of the asymptomatic surveillance period. Therefore the current testing involves uncertainty. The person might be just a carrier or the infection might be cleared by immune system before any symptoms appeared. There were only 44 asymptomatic cases accrued from 3921 individuals, showing that asymptomatic cases are rather rare or have been missed. The VE result based on such testing gave very wide CI, showing the uncertainty. Therefore we cannot

conclude that vaccination protected from carrying the infection without symptoms from this NAAT based analysis.

Vaccine Efficacy in Participants With Evidence of SARS-CoV-2 Infection

For the exploratory efficacy endpoint, VE for BNT162b2 30 µg (2-dose primary series) against asymptomatic SARS-CoV-2 infection was evaluated in participants with evidence of infection up to the start of the asymptomatic surveillance period. Cases were counted from the start of the asymptomatic surveillance period.,

Among participants included in the evaluable efficacy (asymptomatic surveillance) population, 213 participants (80 in BNT162b2 group and 133 in placebo group) had evidence of infection with SARS-CoV-2 prior to the start of the asymptomatic surveillance period. There were 10 asymptomatic SARS-CoV-2 infections in the BNT162b2 (30 µg) group compared to 35 infections reported in the placebo group. The estimated VE was 70.8% (2-sided 95% CI: 39.7%, 87.1%) for BNT162b2. This descriptive analysis was limited by the accrual of only 45 infections total, resulting in a wide 2-sided 95% CI and limiting the precision of this estimate.

VE of BNT162b2 for the same efficacy endpoint based on the Dose 2 all-available efficacy population was 65.6% (2-sided 95% CI: 32.3%, 83.7%).

Table 5: Vaccine Efficacy – Asymptomatic SARS-CoV-2 Infection Based on Central Laboratory–Confirmed NAAT Result – Subjects With Evidence of Infection Prior to the Start of the Asymptomatic Surveillance Period – Evaluable Efficacy (Asymptomatic Surveillance) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=80)		Placebo (N[a]=133)			
Efficacy Endpoint	n[b]	Surveillance Time[c]	n[b]	Surveillance Time[c]	VE (%)	(95% CI[d])
Asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT result during asymptomatic surveillance period	10	0.014	35	0.014	70.8	(39.7, 87.1)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had serological or virological evidence of past SARS-CoV-2 infection (i.e, N-binding antibody [serum] positive at either Visit 1 or asymptomatic surveillance consent visit, or SARS-CoV-2 positive detected by NAAT [nasal swab] at Visits 1 or 2, or had positive NAAT [nasal swab] at any unscheduled visit) prior to the start of the asymptomatic surveillance period were included in the analysis.
a. N = number of subjects in the specified group.
b. n = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group. Time period for case accrual is from the start of the asymptomatic surveillance period to the end of the surveillance period.
d. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adc19nat Table Generation: 18JUL2023 (22:33)
(Snapshot Date: 28APR2023) Output File: ./nda2 unblinded/C4591001 ASYMP CSR/adc19nat ve as nat pd2 eval

Assessor´s comment: A rather high proportion of asymptomatic cases were detected in this small population (45/210). This implicates that Sars-Cov-19 experienced subjects are less likely to develop symptoms during a subsequent infection compared to the first infection. Anyhow, despite of the low numbers, the data shows better protection against asymptomatic infections for subjects who have been infected before vaccination compared to the previously infected but not vaccinated subjects. This phenomenon is described earlier in observational studies, where previous infection in combination with vaccination gave a broader protection against new strains than only infection or only vaccination.

Vaccine Efficacy Against Non-S-Seroconversion to SARS-CoV-2

Asymptomatic Infection Based on N-Binding Antibody Seroconversion

Efficacy Population

The proportions of participants included in the efficacy populations were similar in both vaccine groups. For participants who were excluded from the evaluable efficacy population, the most common reason was because participants did not receive all vaccinations as randomised or did not receive Dose 2 within the predefined window (19 to 42 days after Dose 1), followed by the reason of not having N-binding test result at any post–Dose 2 visit. Among the 44,101 participants included in the evaluable efficacy population, 41,564 participants (90%) had no evidence of infection prior to the first post–Dose 2 N-binding test.

Table 6: Efficacy Populations – Asymptomatic Infection Based on N-Binding Antibody Seroconversion

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	23105 (100.0)	23100 (100.0)	46205 (100.0)
Dose 1 all-available efficacy population	23023 (99.6)	23027 (99.7)	46050 (99.7)
Subjects without evidence of infection prior to the first post–Dose 1 N-binding test[c]	21565 (93.3)	21201 (91.8)	42766 (92.6)
Subjects excluded from Dose 1 all-available efficacy population	82 (0.4)	73 (0.3)	155 (0.3)
Reason for exclusion[d]			
Did not receive at least 1 vaccination	58 (0.3)	51 (0.2)	109 (0.2)
Did not provide informed consent	2 (0.0)	0	2 (0.0)
Data considered potentially unreliable due to lack of PI oversight identified as significant quality event	22 (0.1)	22 (0.1)	44 (0.1)
Dose 2 all-available efficacy population	22705 (98.3)	22646 (98.0)	45351 (98.2)
Subjects without evidence of infection prior to the first post–Dose 2 N-binding test[e]	21376 (92.5)	21032 (91.0)	42408 (91.8)
Subjects excluded from Dose 2 all-available efficacy population	400 (1.7)	454 (2.0)	854 (1.8)
Reason for exclusion[d]			
Did not receive 2 vaccinations	378 (1.6)	439 (1.9)	817 (1.8)
Did not provide informed consent	2 (0.0)	0	2 (0.0)
Data considered potentially unreliable due to lack of PI oversight identified as significant quality event	22 (0.1)	22 (0.1)	44 (0.1)
Evaluable efficacy (seroconversion) population	22032 (95.4)	22069 (95.5)	44101 (95.4)
Subjects without evidence of infection prior to the first post–Dose 2 N-binding test[f]	20872 (90.3)	20692 (89.6)	41564 (90.0)
Subjects excluded from evaluable efficacy (seroconversion) population	1073 (4.6)	1031 (4.5)	2104 (4.6)
Reason for exclusion[d]			
Randomized but did not meet all eligibility criteria	32 (0.1)	26 (0.1)	58 (0.1)
Did not provide informed consent	2 (0.0)	0	2 (0.0)
Data considered potentially unreliable due to lack of PI oversight identified as significant quality event	22 (0.1)	22 (0.1)	44 (0.1)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	726 (3.1)	744 (3.2)	1470 (3.2)
Did not have N-binding test result at any post–Dose 2 visit	505 (2.2)	637 (2.8)	1142 (2.5)
Had other important protocol deviations prior to the first post–Dose 2 N-binding test	248 (1.1)	113 (0.5)	361 (0.8)

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

a. n = Number of subjects with the specified characteristic.

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

c. Includes subjects who had no serological or virological evidence of past SARS-CoV-2 infection before Dose 1 (ie, negative N-binding antibody [serum] result at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1) and had a negative NAAT (nasal swab) result at any unscheduled visit prior to the first post–Dose 1 N-binding test result.

d. Subjects may have been excluded for more than 1 reason.

e. Includes subjects who had no serological or virological evidence of past SARS-CoV-2 infection before Dose 2 (ie, negative N-binding antibody [serum] result at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2) and had a negative NAAT (nasal swab) result at any unscheduled visit prior to the first post–Dose 2 N-binding test result.

f. Includes subjects who had no serological or virological evidence of past SARS-CoV-2 infection before Dose 2 (ie, negative N-binding antibody [serum] result at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2) and had a negative NAAT (nasal swab) result at any unscheduled visit and without any important protocol deviation prior to the first post–Dose 2 N-binding test result.

PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 18JUL2023 (22:33)
(Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_ASYMP_CSR/adsl_eff_pop_as_nig

Table 7: Demographic Characteristics – Subjects Without Evidence of Infection Prior to the First Post–Dose 2 N-Binding Test – Evaluable Efficacy (Seroconversion) Population

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=20872) n[b] (%)	Placebo (N[a]=20692) n[b] (%)	Total (N[a]=41564) n[b] (%)
Sex			
Male	10697 (51.3)	10421 (50.4)	21118 (50.8)
Female	10175 (48.7)	10271 (49.6)	20446 (49.2)
Race			
White	17314 (83.0)	17221 (83.2)	34535 (83.1)
Black or African American	1733 (8.3)	1729 (8.4)	3462 (8.3)
American Indian or Alaska Native	198 (0.9)	177 (0.9)	375 (0.9)
Asian	955 (4.6)	951 (4.6)	1906 (4.6)
Native Hawaiian or other Pacific Islander	50 (0.2)	28 (0.1)	78 (0.2)
Multiracial	547 (2.6)	484 (2.3)	1031 (2.5)
Not reported	75 (0.4)	102 (0.5)	177 (0.4)
All others[c]	1825 (8.7)	1742 (8.4)	3567 (8.6)
Racial Designation			
Japanese	81 (0.4)	75 (0.4)	156 (0.4)
Ethnicity			
Hispanic/Latino	5184 (24.8)	5094 (24.6)	10278 (24.7)
Non-Hispanic/non-Latino	15618 (74.8)	15503 (74.9)	31121 (74.9)
Not reported	70 (0.3)	95 (0.5)	165 (0.4)
Country			
Argentina	2592 (12.4)	2558 (12.4)	5150 (12.4)
Brazil	1313 (6.3)	1288 (6.2)	2601 (6.3)
Germany	236 (1.1)	242 (1.2)	478 (1.2)
South Africa	291 (1.4)	273 (1.3)	564 (1.4)
Turkey	228 (1.1)	216 (1.0)	444 (1.1)
USA	16212 (77.7)	16115 (77.9)	32327 (77.8)
Age group (years)			
12 to 15	1050 (5.0)	1008 (4.9)	2058 (5.0)
16 to 55	11575 (55.5)	11470 (55.4)	23045 (55.4)
>55	8247 (39.5)	8214 (39.7)	16461 (39.6)
≥65	4221 (20.2)	4232 (20.5)	8453 (20.3)
16 to 17	347 (1.7)	328 (1.6)	675 (1.6)
16 to 25	1639 (7.9)	1618 (7.8)	3257 (7.8)
16 to 64	15601 (74.7)	15452 (74.7)	31053 (74.7)
18 to 64	15254 (73.1)	15124 (73.1)	30378 (73.1)
55 to 64	4455 (21.3)	4385 (21.2)	8840 (21.3)
65 to 74	3374 (16.2)	3390 (16.4)	6764 (16.3)
≥75	847 (4.1)	842 (4.1)	1689 (4.1)
75 to 85	842 (4.0)	836 (4.0)	1678 (4.0)
>85	5 (0.0)	6 (0.0)	11 (0.0)
Age at vaccination (years)			
Mean (SD)	48.2 (17.50)	48.2 (17.49)	48.2 (17.49)
Median	50.0	50.0	50.0
Min, max	(12, 89)	(12, 91)	(12, 91)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence of past SARS-CoV-2 infection before Dose 2 (ie, negative N-binding antibody [serum] result at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2) and had a negative NAAT (nasal swab) result at any unscheduled visit and without any important protocol deviation prior to the first post–Dose 2 N-binding test result were included in the analysis.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 22JUN2023 (11:05)
(Cutoff Date: , Snapshot Date: 28APR2023) Output File:
./nda2 unblinded/C4591001 ASYMP CSR/adsl demo as nig eval eff

VE against non-S-seroconversion to SARS-CoV-2 infection Result

For the secondary efficacy endpoint, VE for BNT162b2 30 µg (2-dose primary series) against non-S-seroconversion to SARS-CoV-2 infection was evaluated in participants without evidence of infection or confirmed COVID-19. Note that the surveillance time in the placebo group was shorter than in the BNT162b2 group and accounted for in the VE calculations. This difference is due to the placebo crossover resulting in a shorter duration of follow up for participants who originally received placebo.

Among participants included in the evaluable efficacy (seroconversion) population, 41564 participants (20872 in BNT162b2 group and 20692 in placebo group) did not have evidence of infection with SARS-CoV-2 prior to the first post–dose 2 N-binding test. There were 612 cases of seroconversion of N-binding antibody, indicative of SARS-CoV-2 infection, in the BNT162b2 (30 µg) group compared to 608 cases in the placebo group. The estimated VE was 52.9% (2-sided 95% CI: 47.2%, 57.9%) for BNT162b2.

VE of BNT162b2 for the same efficacy endpoint based on the Dose 1 and Dose 2 all-available efficacy populations was 49.7% (2-sided 95% CI: 44.0%, 54.9%) and 52.3% (2-sided 95% CI: 46.7%, 57.3%), respectively.

Table 8: Vaccine Efficacy – Asymptomatic Infection Based on N-Binding Antibody Seroconversion – Subjects Without Evidence of Infection Prior to the First Post–Dose 2 N-Binding Test – Evaluable Efficacy (Seroconversion) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=20872)		Placebo (N[a]=20692)			
Efficacy Endpoint	n[b]	Surveillance Time[c]	n[b]	Surveillance Time[c]	VE (%)	(95% CI[d])
Asymptomatic infection based on N-binding antibody seroconversion after Dose 2	612	13.840	608	6.481	52.9	(47.2, 57.9)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence of past SARS-CoV-2 infection before Dose 2 (ie, negative N-binding antibody [serum] result at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2) and had a negative NAAT (nasal swab) result at any unscheduled visit and without any important protocol deviation prior to the first post–Dose 2 N-binding test result were included in the analysis.
a. N = number of subjects in the specified group.
b. n = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group. Time period for case accrual is from Dose 2 to the end of the surveillance period.
d. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adc19asm Table Generation: 18JUL2023 (22:31)
(Snapshot Date: 28APR2023) Output File: ./nda2 unblinded/C4591001 ASYMP CSR/adc19asm ve as nig pd2 eval

In the evaluable efficacy (seroconversion) population without evidence of SARS-CoV-2 infection, VE of BNT162b2 was 60.4% and 56.6% from Dose 2 to 1 month after Dose 2 and from >1 month after Dose 2, respectively. The VE for cases confirmed after Dose 2 was 52.9% (2-sided 95% CI: 47.2%, 57.9%) based on 612 and 608 cases in the BNT162b2 (30 µg) and placebo groups, respectively. Note that >1 month after Dose 2, the surveillance time in the BNT162b2 (30 µg) group (11.961 [1000 person-years]) was more than twice the surveillance time in the placebo group (4.681 [1000 person-years]),

which is accounted for in the VE calculations; this is due to the placebo crossover resulting in truncated follow-up time for participants who originally received placebo.

Table 9: Vaccine Efficacy by Time Interval – Asymptomatic Infection Based on N-Binding Antibody Seroconversion – Subjects Without Evidence of Infection – Evaluable Efficacy (Seroconversion) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg)		Placebo			
Efficacy Endpoint Subgroup	N[a]/n[b]	Surveillance Time[c]	N[a]/n[b]	Surveillance Time[c]	VE (%)	(95% CI[d])
Asymptomatic infection based on N-binding antibody seroconversion after Dose 2	20872/612	13.840	20692/608	6.481	52.9	(47.2, 57.9)
Dose 2 to 1 month after Dose 2	20697/34	1.750	20502/85	1.734	60.4	(40.4, 74.2)
>1 Month after Dose 2	19487/576	11.961	18012/519	4.681	56.6	(51.0, 61.5)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence of past SARS-CoV-2 infection before Dose 2 (ie, negative N-binding antibody [serum] result at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2) and had a negative NAAT (nasal swab) result at any unscheduled visit and without any important protocol deviation prior to the first post–Dose 2 N-binding test result were included in the analysis.
Note: Subjects who don't have a post–Dose 2 N-binding test at 1 month after Dose 2 or upto 42 days from Dose 2 were not included in the subgroup rows for time-interval analysis.
a. N = number of subjects in the specified group.
b. n = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group. Time period for case accrual is from Dose 2 to the end of the surveillance period for the overall row and from the start to the end of the ranges for each time interval.
d. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adc19asm Table Generation: 24JUL2023 (15:11)
(Snapshot Date: 28APR2023) Output File: ./nda2 unblinded/C4591001 ASYMP CSR/adc19asm ve as nig pd2 ti eval

Assessor´s comment: An impressive number of participants (more than 40,000) have been sampled for blood after 1, 6, 12, and 24 months post dose 2 and tested for N- protein specific antibodies, which is a marker for natural SARS-CoV-2 infection regardless of the strain. The seroconversion to N-protein is a stable biomarker for passed SARS-CoV-2 infection and therefore this analysis gives a reliable estimate of infection. The follow-up time for the placebo arm was about half compared to the active arm, which might introduce a biased analysis. The results of the N-antibody seroconversion analysis indicate that Comirnaty Original 30 provided protection against asymptomatic infections after 2 doses.

Incidence Rates of First COVID-19 Occurrence After Vaccination

Analyses were performed for COVID-19 cases accrued for the following groups and periods:

- Original BNT162b2 (30 µg) group during a period when multiple SARS-CoV-2 strains were circulating (ie, original/wild type strain and Alpha, Beta, Delta, Gamma, Omicron variants), pre-dominating at various times during the period from the Dose 1 vaccination date to the earliest of confirmed case, death, study withdrawal, study completion date, or the participant's first dose of BNT162b2$_{SA}$ vaccine.

- Original placebo prior to crossover group for the time between vaccination in the blinded period, and the crossover date. The original/wild type was the predominant strain during this period. Most of the Phase 2/3 participants were unblinded (April 2021) and transitioned to the crossover group when the Delta variant was the predominant strain. Crossover of Phase 2/3 participants was completed by October 2021.
- Placebo crossover to BNT162b2 (30 µg) group for the period from first BNT162b2 vaccination. Analyses were performed for COVID-19 cases accrued for the placebo crossover to BNT162b2 (30 µg) group when Alpha and Beta variants (01 December 2020 to 10 January 2021), Gamma variant (11 January 2021 to 03 April 2021), Delta variant (04 April 2021 to 26 November 2021), Omicron variant (27 November 2021 to LSLV) were predominant.

For cases of first COVID-19 occurrence after vaccination, the IRs for participants in the original BNT162b2, original placebo prior to crossover, and placebo crossover to BNT162b2 groups were 104.562, 125.722, and 169.138 per 1000 person-years of follow-up, respectively.

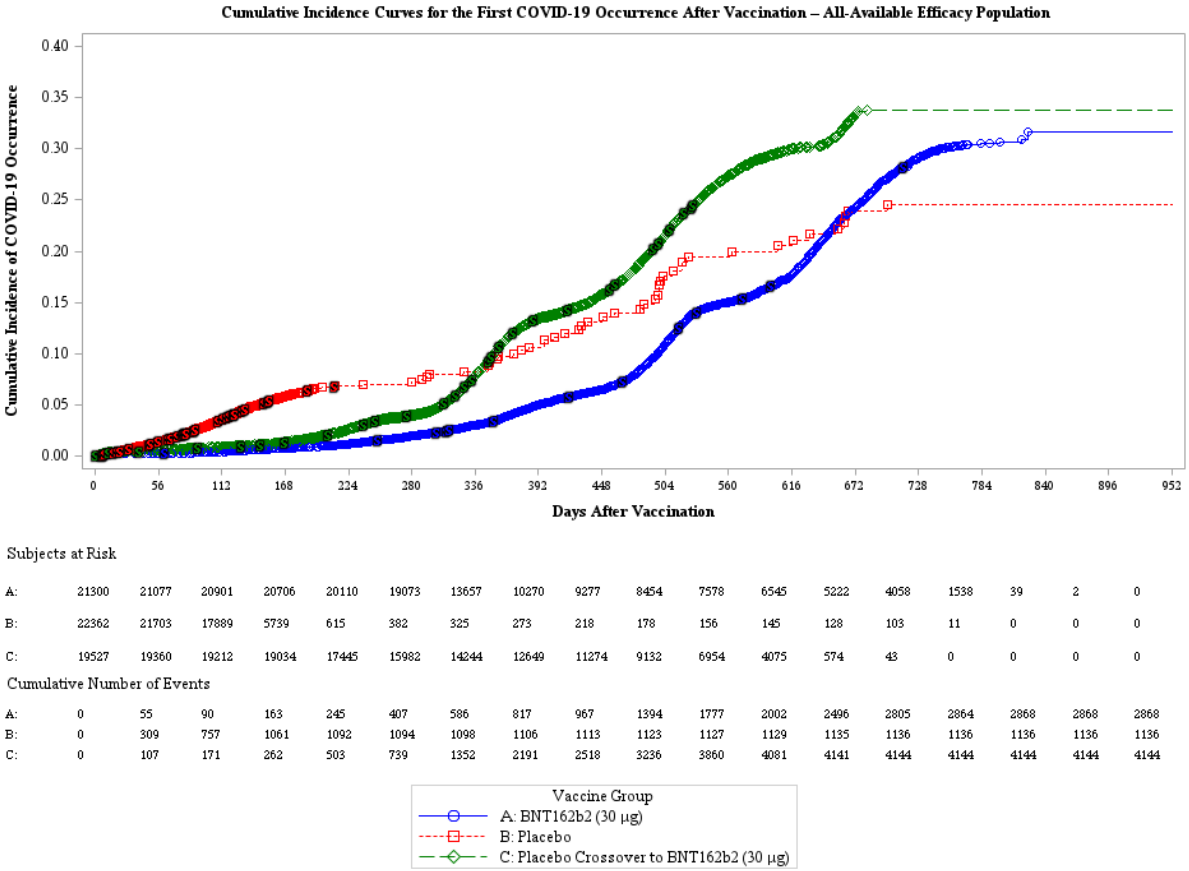
Table 10: Incidence Rates of First COVID-19 Occurrence After Vaccination – All-Available Efficacy Population

	Vaccine Group								
	Original BNT162b2 (30 µg)			Original Placebo Prior to Crossover			Placebo Crossover to BNT162b2 (30 µg)		
Efficacy Endpoint	n1[a]	Surveillance Time[b] (n2[c])	IR (/1000 PY)[d]	n1[a]	Surveillance Time[b] (n2[c])	IR (/1000 PY)[d]	n1[a]	Surveillance Time[b] (n2[c])	IR (/1000 PY)[d]
First COVID-19 occurrence after vaccination	2868	27.429 (21300)	104.562	1136	9.036 (22362)	125.722	4144	24.501 (19527)	169.138

a. n1 = Number of participants meeting the endpoint definition.
b. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. For the original BNT162b2 arm, time period for COVID-19 case accrual is from the dose 1 vaccination date to the earliest of confirmed case, death, withdrawn from the study, study completion date, or their first dose of BNT162b2SA vaccination. For original Placebo arm, the time period between vaccination in blinded period and the crossover date is considered. For the Placebo crossover to BNT162b2 (30 µg) arm, the time period from first BNT162b2 vaccination is considered as the starting point for surveillance.
c. n2 = Number of participants at risk for the endpoint.
d. Incidence rate (IR) is calculated as number of participants meeting the endpoint definition/total surveillance time across all participants at risk for the endpoint within the specific group.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adc19eu Table Generation: 17MAY2023 (00:35)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adc19ef_ve_overall_d1_aai

Kaplan-Meier curve shows the case accrual from vaccination up to the end of study date for the participants who received BNT162b2 originally (original BNT162b2 group), participants who received placebo originally prior to crossover (original placebo group), and participants who received placebo originally and then crossed over to receive BNT162b2 (placebo crossover to BNT162b2 group), with severe COVID-19 cases denoted with 'S' on the curves. During the entire study period, most participants were eligible to receive up to 4 vaccine doses (2 dose primary series and 2 booster doses). In the postvaccination period, there is clear evidence of better protection by BNT162b2 compared to placebo in the immediate months following vaccination before cross over occurred. After placebo crossover, case accrual increased for both the original BNT162b2 and placebo crossover groups following different variant waves. The curves steepen substantially around 470 and 300 days for the original BNT162b2 and placebo crossover groups, respectively, which likely represents when each group was exposed to the start of the Omicron waves.

Figure 2: Cumulative Incidence Curves for the First COVID-19 Occurrence After Vaccination – All Available Efficacy Population



Note: "S" indicates participants with severe COVID-19.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adc19eu Table Generation: 17MAY2023 (00:40)
(Database Snapshot Date: 28APR2023) Output File: /nda2_unblinded/C4591001_CSR/adc19ef_f001_kmx_aai

Assessor´s comment: The current results illustrate the VE over the 2 years of pandemic, where different new SARS-CoV-2 strains evolved over a short time window and Original Comirnaty became less immunogenically cross-reactive with the circulating strains. The Original Comirnaty was very effective in the beginning of the pandemic. After the authorisation, the placebo arm were offered vaccination and became a cross-over arm. The active arm were offered more doses as the study continued with booster doses. The cross over arm also received boosters, but with at a later time point and therefore had received fewer doses than the original active arm every time a new strain appeared. Thus, the results are not easily interpretable but are in agreement with waning protection to new variants.

The MAH Summary of Efficacy

A formal secondary efficacy analysis was performed to assess vaccine efficacy against asymptomatic SARS-CoV-2 infections and against non-S-seroconversion to SARS-CoV-2. The incidence of confirmed first COVID-19 through the entire study follow-up period in participants who received BNT162b2 was also described.

- In the evaluable efficacy (asymptomatic surveillance) population without evidence of SARS-CoV-2 infection prior to the start of the asymptomatic surveillance period, the VE for BNT162b2 30 µg (2-dose primary series) based on NAAT-confirmed infection was 37.2% (2-sided 95% CI: -20.0%, 66.7%) based on 24 asymptomatic SARS-CoV-2 infections in the BNT162b2 group and 20 infections reported in the placebo group.
- In the evaluable efficacy (asymptomatic surveillance) population with evidence of SARS-CoV-2 infection prior to the start of the asymptomatic surveillance period, the VE for BNT162b2 30 µg (2-dose primary series) was 70.8% (2-sided 95% CI: 39.7%, 87.1%) based on 10 asymptomatic SARS-CoV-2 infections in the BNT162b2 group and 35 infections reported in the placebo group.
- In the evaluable efficacy (seroconversion) population without evidence of SARS-CoV-2 infection prior to the first post–Dose 2 N-binding test, the VE for BNT162b2 30 µg (2-dose primary series) was 52.9% (2-sided 95% CI: 47.2%, 57.9%) for confirmed cases. From Dose 2 to 1 month after Dose 2 and from >1 month after Dose 2, the VE was 60.4% and 56.6%, respectively, and the overall VE was 52.9% (2-sided 95% CI: 47.2%, 57.9%) after Dose 2.
- Confirmed COVID-19 cases accrued through the entire study follow-up as multiple SARS-CoV-2 variants circulated, most notably following the emergence of Omicron. Incidence Rates for participants in the original BNT162b2, original placebo prior to crossover, and placebo crossover to BNT162b2 groups were 104.562, 125.722, and 169.138 per 1000 person-years of follow-up, respectively. This prompted the development and implementation of variant-adapted vaccines: bivalent vaccines targeting the original/wild type strain and Omicron BA.1 or BA.4/BA.5, and most recently monovalent XBB.1.5.

6.2.2. Immunogenicity

Phase 3

Summarised below are immunogenicity results for Phase 3 BNT162b2-experienced participants, 18 through 55 and >55 years of age, who received a lower booster dose (Dose 3) of BNT162b2 (5 or 10 µg).

Immunogenicity Populations

The immunogenicity populations of BNT162b2-experienced participants who were rerandomised to receive a booster dose of BNT162b2 (5 or 10 µg) instead of approved dose of 30 µg are presented below. One participant each was excluded from the Dose 3 booster evaluable immunogenicity population for not having at least 1 valid and determinate immunogenicity result within 28-42 days after booster vaccination in the BNT162b2 (5 µg) >55 years of age group and the BNT162b2 (10 µg) 18 through 55 years and >55 years of age groups. One additional participant in the BNT162b2 (5 µg) >55 years of age group was excluded from the Dose 3 booster evaluable immunogenicity population due to having an important protocol deviation(s) as determined by the clinician. The demographics of the small immunogenicity population is presented also below.

Table 11: Immunogenicity Populations – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose)

	Vaccine Group (as Randomized)			
	BNT162b2 (5 µg)		BNT162b2 (10 µg)	
	18- 55 Years n[a] (%)	>55 Years n[a] (%)	18- 55 Years n[a] (%)	>55 Years n[a] (%)
Rerandomized[b]	26 (100.0)	53 (100.0)	25 (100.0)	51 (100.0)
Dose 3 booster all-available immunogenicity population	26 (100.0)	53 (100.0)	25 (100.0)	51 (100.0)
Dose 3 booster evaluable immunogenicity population	26 (100.0)	51 (96.2)	24 (96.0)	50 (98.0)
Without evidence of infection up to 1-month post–booster dose[c]	24 (92.3)	47 (88.7)	24 (96.0)	48 (94.1)
Subjects excluded from Dose 3 booster evaluable immunogenicity population	0	2 (3.8)	1 (4.0)	1 (2.0)
Reason for exclusion[d]				
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after booster vaccination	0	1 (1.9)	1 (4.0)	1 (2.0)
Had important protocol deviation(s) as determined by the clinician	0	1 (1.9)	0	0

a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Subjects who had no serological or virological evidence (up to 1 month after receipt of the booster vaccination) of past SARS-CoV-2 infection
(ie, N-binding antibody [serum] negative at Dose 1 visit, 1-month post–Dose 2 visit, booster dose visit, 1-month post–booster visit and SARS-CoV-2
not detected by NAAT [nasal swab] at Dose 1 visit, Dose 2 visit, booster dose visit) and had a negative NAAT (nasal swab) at any unscheduled visit
up to 1 month after booster vaccination were included in the analysis.
d. Subjects may have been excluded for more than 1 reason.
PFIZER CONFIDENTIAL SDTM Creation: 14DEC2021 (00:12) Source Data: adsl Table Generation: 20JAN2022 (01:47)
(Data Cutoff Date: 22NOV2021, Database Snapshot Date: 10DEC2021) Output File:
./nda2 unblinded/C4591001 G4 LD/adva s008 imm g4 6m

Table 12: Demographic Characteristics – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose) – Dose 3 Booster Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)			
	BNT162b2 (5 µg)		BNT162b2 (10 µg)	
	18-55 Years (N[a]=26) n[b] (%)	>55 Years (N[a]=51) n[b] (%)	18-55 Years (N[a]=24) n[b] (%)	>55 Years (N[a]=50) n[b] (%)
Sex				
Male	13 (50.0)	29 (56.9)	15 (62.5)	20 (40.0)
Female	13 (50.0)	22 (43.1)	9 (37.5)	30 (60.0)
Race				
White	16 (61.5)	38 (74.5)	16 (66.7)	38 (76.0)
Black or African American	3 (11.5)	3 (5.9)	3 (12.5)	2 (4.0)
Asian	4 (15.4)	10 (19.6)	4 (16.7)	7 (14.0)
Native Hawaiian or other Pacific Islander	1 (3.8)	0	1 (4.2)	0
Multiracial	2 (7.7)	0	0	2 (4.0)
Not reported	0	0	0	1 (2.0)
Racial designation				
Japanese	0	1 (2.0)	0	3 (6.0)
Ethnicity				
Hispanic/Latino	6 (23.1)	4 (7.8)	3 (12.5)	4 (8.0)
Non-Hispanic/non-Latino	20 (76.9)	47 (92.2)	21 (87.5)	46 (92.0)
Country				
USA	26 (100.0)	51 (100.0)	24 (100.0)	50 (100.0)
Age at booster vaccination (years)				
Mean (SD)	40.2 (8.63)	64.5 (6.27)	40.3 (10.86)	64.0 (5.86)
Median	40.0	63.0	42.0	62.5
Min, max	(25, 55)	(56, 83)	(19, 55)	(56, 79)
Body mass index (BMI)				
Underweight (<18.5 kg/m^2)	0	0	0	1 (2.0)
Normal weight (≥18.5-24.9 kg/m^2)	8 (30.8)	11 (21.6)	9 (37.5)	18 (36.0)
Overweight (≥25.0-29.9 kg/m^2)	10 (38.5)	25 (49.0)	6 (25.0)	19 (38.0)
Obese (≥30.0 kg/m^2)	8 (30.8)	15 (29.4)	9 (37.5)	12 (24.0)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 14DEC2021 (00:12) Source Data: adsl Table Generation: 13JAN2022 (21:36)
(Data Cutoff Date: 22NOV2021, Database Snapshot Date: 10DEC2021) Output File: ./nda2 unblinded/C4591001 G4 LD/adsl s005 g4 6m eval

SARS-CoV-2 Neutralising Titres to Reference Strain

GMTs

Among participants in the Dose 3 evaluable immunogenicity population without evidence of SARS-CoV-2 infection up to 1 month after the booster dose, SARS-CoV-2 50% neutralising GMTs increased substantially at 1 month (Day 28) after the booster (Dose 3) for both dose and age groups (table below). The SARS-CoV-2 50% neutralising GMTs were similar, immediately before and 1 month after booster dose across the dose and age groups.

Similar results were observed for participants in the booster (Dose 3) evaluable immunogenicity population regardless of prior infection status and for participants in the Dose 3 booster all-available immunogenicity population.

Table 13: Geometric Mean Titres – Phase 3 – BNT162b2-Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose) – Dose 3 Booster Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		BNT162b2 (5 µg)				BNT162b2 (10 µg)			
		18-55 Years		>55 Years		18-55 Years		>55 Years	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	3/Prevax	24	100.3 (64.9, 155.1)	47	88.6 (69.1, 113.5)	24	88.4 (65.6, 119.1)	48	83.2 (66.9, 103.3)
	3/1 Month	24	905.7 (689.7, 1189.4)	47	978.8 (790.9, 1211.3)	24	980.3 (749.6, 1282.1)	48	1030.6 (830.3, 1279.2)

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; Prevax = prevaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of the booster vaccination) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Dose 1 visit, 1-month post–Dose 2 visit, booster dose visit, 1-month post–booster visit and SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 visit, Dose 2 visit, booster dose visit) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL SDTM Creation: 16FEB2022 (11:21) Source Data: adva Table Generation: 17FEB2022 (20:53)
(Data Cutoff Date: 22NOV2021, Database Snapshot Date: 10DEC2021) Output File: ./nda3_unblinded/C4591001_G4_IMM/adva_s001_gm_g4_6mcf_evl

Assessor´s comment: the majority of this immunology population did not have signs of previous infection with SARS-CoV-2. Unfortunately, here was not direct comparison to the approved 30 µg dose investigated. Anyhow, the pre 3-dose titre was similar to the earlier reported 30 µg age group. After the 3rd dose with 5 or 10 µg, the titres were very similar to each other, around 900- 1000. The earlier data for 30 µg dose show titre above 2000, 1 month post-dose 3. We can conclude that lower dose for adults is immunogenic, but the 30 µg is more suitable.

The earlier results for Original Comirnaty 30 µg:

Geometric Mean Titres – Phase 3 – BNT162b2-Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (30µg)– Dose 3 Booster Evaluable Immunogenicity Population

Assay	Dose/ Sampling Time Point[a]	Vaccine Group (as Randomized) BNT162b2 (30 µg) n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	1/Prevax	217	20.8 (20.2, 21.5)
	2/1 Month	214	767.2 (670.2, 878.2)
	3/Prevax	213	134.4 (119.8, 150.9)
	3/Day 7	108	1418.7 (1263.3, 1593.3)
	3/1 Month	232	2374.2 (2134.1, 2641.3)

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; Prevax = prevaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1, 3, 301, and 303 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1, 2, and 301) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL SDTM Creation: 02FEB2022 (17:13) Source Data: adva Table Generation: 05FEB2022

GMFRs

Among participants in the Dose 3 booster evaluable immunogenicity population without evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3), the GMFR of SARS-CoV-2 50% serum neutralising titres 1 month after Dose 3 ranged from 9.0 to 12.4 (median time 6.8 to 7.2 months from Dose 2 to booster [Dose 3]) in the BNT162b2 (5 or 10 µg) groups. Of note, GMFR of SARS-CoV-2 50% serum neutralising titre from before Dose 3 to 1 month after Dose 3 of BNT162b2 30 µg was 17.7 (median time 6.8 months from Dose 2 to booster [Dose 3]) (20 May 2022 interim CSR), indicating a higher booster effect of the 30-µg dose than the lower doses (5 or 10 µg).

The GMFRs were similar for participants in the booster (Dose 3) evaluable immunogenicity population regardless of prior infection status and for participants in the booster (Dose 3) all-available immunogenicity population.

Table 14: Geometric Mean Fold Rise From Before Booster Dose to Each Subsequent Time Point – Phase 3 – BNT162b2-Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose) – Dose 3 Booster Evaluable Immunogenicity Population

Assay	Dose/ Sampling Time Point[a]	Vaccine Group (as Randomized)							
		BNT162b2 (5 µg)				BNT162b2 (10 µg)			
		18-55 Years		>55 Years		18-55 Years		>55 Years	
		n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	3/1 Month	24	9.0 (6.0, 13.6)	47	11.0 (8.4, 14.6)	24	11.1 (8.2, 15.0)	48	12.4 (9.2, 16.7)

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of the booster vaccination) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Dose 1 visit, 1-month post–Dose 2 visit, booster dose visit, 1-month post–booster visit and SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 visit, Dose 2 visit, booster dose visit) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified assay at both prevaccination time point and 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.
PFIZER CONFIDENTIAL SDTM Creation: 16FEB2022 (11:21) Source Data: adva Table Generation: 17FEB2022 (20:53)
(Data Cutoff Date: 22NOV2021, Database Snapshot Date: 10DEC2021) Output File: ./nda3_unblinded/C4591001_G4_IMM/adva_s002_gmfr_g4_6mcf_evl

Assessor´s comment: By 1 month after Dose 3, the GMFR from before Dose 3 was 17.6 (2-sided 95% CI: 15.3, 20.2), which is higher than after 5 or 10 µg. No correlate of protection has been identified, but it is assumed that higher neutralising antibody titres likely correlates with increased protection, and therefore it can be concluded that the Original Comirnaty 30 µg is an adequate dose for a booster for adults as it resulted in higher titres than in case of lower doses.

The MAH Summary of Immunogenicity

Lower booster doses of BNT162b2 (5 or 10 µg) in BNT162b2-experienced participants substantially increased SARS-CoV-2 neutralising antibody response 1 month after Dose 3 in participants 18 through 55 and >55 years of age, based on GMTs, GMFRs, and Reverse Cumulative Incidence Curves (RCDCs). Although there is no contemporaneous 30-µg comparator for lower booster doses of BNT162b2 (5 or 10 µg), the GMFR for 30-µg booster (Phase 3), presented in the 20 May 2022 interim CSR, show that, based on GMFR values, a higher booster dose of BNT162b2 elicits a more robust immune response.

6.3. Discussion

Study C4591001 is a Phase 1/2/3 multicentre, multinational, randomised, placebo-controlled, observer-blind, dose finding, vaccine candidate-selection, and efficacy study in healthy individuals ≥12 years of age. This report includes the final data from study C4591001. The study including more than 40,000 individuals. They received 2 doses of Original Comirnaty 30 µg, and were followed up for up to 2 years post-dose 2. Originally, the study had an active arm and a placebo arm, but after the approval of the vaccine, the placebo arm was offered vaccination thus creating a cross-over arm and the study became unblinded. The study continued with options to receive booster doses with the Original vaccine (3 and 4th dose) in all groups. The surveillance for COVID-19 continued during the entire study period, up to 2 years post-dose 2. Also, participants gave 3-5 blood samples to monitor for seroconversion

after possible infection (N-antigen antibody detection).

In the current final report, the MAH presents data from asymptomatic infection surveillance during the entire study period and also an immunogenicity analysis of a third dose of BNT162b2 at a lower dose of 5 or 10 µg administered to smaller population of Phase 2/3 participants.

The asymptomatic infection surveillance was performed using two distinct biomarkers: NAAT in a subpopulation (N= 4000) and N-protein detection in the entire population (N= 40 000). The time window to detect viral RNA was limited. The surveillance for asymptomatic infections did not start immediately after the vaccination. The median time between Dose 2 and the start of the asymptomatic surveillance period was 2.9 months for participants in the United States and 5.3 months for participants in Argentina. Cases were counted from the start of the asymptomatic surveillance period. Therefore, the current testing for NAAT involves uncertainties. There were only 44 asymptomatic cases accrued from 3921 individuals, showing that asymptomatic cases are rather rare or have been missed. The VE result based on a such testing gave a wide CI, VE = 37.2% (95% CI: -20.0%; 66.7%).

Interestingly, a rather high proportion of asymptomatic cases were detected among the previously infected population (45 asymptomatic cases out of 210 subjects). Although the sample size was small, it appears that a COVID-19 experienced population are at lower risk to develop symptoms during a subsequent infection compared to the first infection. Also, despite low numbers, the data showed better protection against asymptomatic infections for subjects who have been infected before vaccination compared to the earlier infected but unvaccinated subjects: VE = 70.8% (95% CI: 39.7%; 87.1%). This phenomenon is described earlier in observational studies, where previous infection in combination with vaccination gave a broader protection against new strains compared to only infection or only vaccination.

The N-protein specific antibodies are stable, long-lasting markers for natural SARS-CoV-2 infection regardless of the virus strain. The entire study population (N= 40,000) was sampled for blood after 1-, 6, 12-, and 24-months post-dose 2 and tested for the seroconversion to the N-protein.

Seroconversion to the N-protein is a stable biomarker for past SARS-CoV-2 infection and therefore this analysis gives a reliable estimate of infection. The follow-up time for the placebo arm was about half compared to the active arm, which might introduce a biased analysis. The results of the N-antibody seroconversion analysis indicated that Comirnaty Original 30 provided protection against asymptomatic infections after 2 doses. The N-antibody seroconversion analysis showed that Comirnaty Original 30 µg provided protection against asymptomatic infections after 2 doses during the study period: VE = 52.9% (95% CI: 47.2%; 57.9%).

The current results illustrate the VE over the 2 years of pandemic, where different new SARS-CoV-2 strains evolved over a short time window and Original Comirnaty became less immunogenically cross-reactive with the circulating strains. The Original Comirnaty was very effective in the beginning of the pandemic. After the authorisation, the placebo arm were offered vaccination and became a cross-over arm. The active arm were offered more doses as the study continued with booster doses. The cross-over arm also received boosters, but with at a later time point and therefore had received fewer doses than the original active arm every time a new strain appeared. Thus, the results are not easily interpretable but are in agreement with waning protection to new variants.

The MAH submitted also immunogenicity results for Phase 3 BNT162b2-experienced participants, 18 through 55 (N= 25) and >55 years of age (N= 55), who received a lower booster dose (Dose 3) of BNT162b2 (5 or 10 µg). Lower booster doses of BNT162b2 substantially increased SARS-CoV-2 neutralising antibody response 1 month after Dose 3, based on GMTs, GMFRs, and RCDCs. Although there was no contemporaneous 30-µg comparator for lower booster doses the GMFR for 30-µg booster (Phase 3), presented earlier showed that a higher booster dose of BNT162b2 elicits a more robust

immune response (GMFR 30-µg = 17; 10 -µg= 12; 5 -µg= 11 for > 55 yoa). Therefore the usage of 30-µg for booster is accurate.

In conclusions, the MAH has presented the final report of study C4591001, with new information about 2 dose Original Comirnaty 30µg VE against asymptomatic infections, incidents rate during the entire 2 years of follow up and boosting effect of the lower doses for adults. The results show that 2 doses of Original Comirnaty provided protection against asymptomatic infections, the Original Active arm was better protected than Placebo or Placebo cross-over arm during the evolving pandemic and that also lower doses of Original Comirnaty have boosting effect for adults.

No changes to the section 5.1 in the SmPC are suggested and we agree.

7. Clinical Safety aspects

7.1. Methods

Study C4591001 was a Phase 1/2/3, multicentre, multinational, randomised, placebo-controlled, observer-blind, dose finding, vaccine candidate–selection, and efficacy study in healthy individuals ≥12 years of age. The study consisted of 2 parts: Phase 1 to identify preferred vaccine candidate(s) and dose level(s) in individuals 18 through 55 and 65 through 85 years of age; and Phase 2/3 as an expanded cohort and efficacy part in individuals ≥12 years of age.

This report includes final results from study C4591001 and interim data for subjects aged 12-15 years who had received one booster dose of BNT162b2 30µg. Based on these data, update of section 4.8 in the SmPC has been proposed by the MAH.

7.1.1. Phase 1

Disposition and Exposure

Disposition of all randomised Phase 1 participants is presented in the table below. All randomised participants received 2 doses and completed the 1-month post–Dose 2 visit during the blinded, placebo-controlled period. Note that for the BNT162b1 100-µg group, the internal review committee (IRC) determined not to administer the second dose of 100 µg to this group of participants due to reactogenicity and as per IRC decision, these participants were instead given Dose 2 of BNT162b1 at the 10-µg dose level. During the open-label follow-up period, 25.0% to 100.0% of participants originally randomised to receive BNT162b1 or BNT162b2, completed the 6-month post–Dose 2 visit. Most participant withdrawals were due to either no longer meeting eligibility criteria or protocol deviations.

Table 15: Disposition of All Randomised Subjects – From Dose 1 to Before Booster Dose – Phase 1 Subjects

	Vaccine Group (as Randomized)								
	BNT162b1				BNT162b2				
	10µg (N[a]=24) n[b] (%)	20µg (N[a]=24) n[b] (%)	30µg (N[a]=24) n[b] (%)	100µg (N[a]=12) n[b] (%)	10µg (N[a]=24) n[b] (%)	20µg (N[a]=24) n[b] (%)	30µg (N[a]=24) n[b] (%)	Placebo (N[a]=39) n[b] (%)	Total (N[a]=195) n[b] (%)
Randomized	24 (100.0)	24 (100.0)	24 (100.0)	12 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	39 (100.0)	195 (100.0)
Not vaccinated	0	0	0	0	0	0	0	0	0
Original blinded, placebo-controlled follow-up period									
Vaccinated	24 (100.0)	24 (100.0)	24 (100.0)	12 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	39 (100.0)	195 (100.0)
Dose 1	24 (100.0)	24 (100.0)	24 (100.0)	12 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	39 (100.0)	195 (100.0)
Dose 2	24 (100.0)	24 (100.0)	24 (100.0)	12 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	39 (100.0)	195 (100.0)
Discontinued from the original blinded, placebo-controlled vaccination period[c]	0	0	0	0	0	0	0	0	0
Unblinded before the 1-month post–Dose 2 visit	0	0	0	0	0	0	0	0	0
Completed the 1-month post–Dose 2 visit	24 (100.0)	24 (100.0)	24 (100.0)	12 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	39 (100.0)	195 (100.0)
Completed the study	0	0	0	0	0	0	0	0	0
Withdrawn from the study	0	0	0	0	0	0	0	0	0
Open-label follow-up period									
Originally randomized to BNT162b1/BNT162b2	24 (100.0)	24 (100.0)	24 (100.0)	12 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)		
Received Dose 2/unplanned dose	0	0	0	0	0	0	0		
Completed the 1-month post–Dose 2 visit	0	0	0	0	0	0	0		
Completed the 6-month post–Dose 2 visit	6 (25.0)	19 (79.2)	8 (33.3)	12 (100.0)	16 (66.7)	12 (50.0)	21 (87.5)		
Withdrawn from the study	3 (12.5)	0	0	3 (25.0)	1 (4.2)	1 (4.2)	0		
Withdrawn before the 6-month post–Dose 2 visit	0	0	0	0	0	0	0		
Withdrawn after the 6-month post–Dose 2 visit	3 (12.5)	0	0	3 (25.0)	1 (4.2)	1 (4.2)	0		
Reason for withdrawal from the study									
Protocol deviation	1 (4.2)	0	0	2 (16.7)	0	1 (4.2)	0		
No longer meets eligibility criteria	2 (8.3)	0	0	1 (8.3)	1 (4.2)	0	0		
Originally randomized to placebo								39 (100.0)	
Withdrawn from the study after unblinding and before receiving BNT162b2								3 (7.7)	
Received first dose of BNT162b2 [30 µg]								35 (89.7)	
Received second dose of BNT162b2 [30 µg]								35 (89.7)	
Discontinued from the open-label vaccination period[d]								0	
Completed the 1-month post–second dose of BNT162b2 visit								35 (89.7)	
Withdrawn from the study								5 (12.8)	
Withdrawn after first dose of BNT162b2 and before second dose of BNT162b2								0	
Withdrawn after second dose of BNT162b2 and before the 1-month post–second dose of BNT162b2 visit								0	
Withdrawn after the 1-month post–second dose of BNT162b2 visit								5 (12.8)	
Reason for withdrawal from the study									
No longer meets eligibility criteria								4 (10.3)	
Protocol deviation								1 (2.6)	

a. N = number of randomized subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Original blinded, placebo-controlled vaccination period: from Dose 1 to the 1-month post–Dose 2 visit.
d. Open-label vaccination period: from first dose of BNT162b2 [30 µg] to the 1-month post–second dose of BNT162b2 [30 µg] visit.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adds Table Generation: 05MAY2023 (01:28)
(Database Snapshot Date: 28APR2023) Output File: ./nda2 unblinded/C4591001 CSR/adds s002 p1

Disposition of Participants Who Received Booster Dose of BNT162b2

Disposition of all Phase 1 participants who received the first booster dose (Dose 3) of BNT162b2 (30 µg) and an additional booster dose (Dose 4) of BNT162b2 (30 µg) is presented below. The population analysed include the number of subjects described below.

Table 16: Disposition of Subjects – Phase 1 – Subjects Who Received Booster Dose of BNT162b2 (30 µg)

	Initial Vaccine Group (as Administered)								
	BNT162b1				BNT162b2				
	10µg (N[a]=21) n[b] (%)	20µg (N[a]=24) n[b] (%)	30µg (N[a]=24) n[b] (%)	100µg (N[a]=9) n[b] (%)	10µg (N[a]=22) n[b] (%)	20µg (N[a]=23) n[b] (%)	30µg (N[a]=24) n[b] (%)	Placebo (N[a]=28) n[b] (%)	Total (N[a]=175) n[b] (%)
Received the first booster vaccination	21 (100.0)	24 (100.0)	24 (100.0)	9 (100.0)	22 (100.0)	23 (100.0)	24 (100.0)	28 (100.0)	175 (100.0)
Completed the first booster vaccination period[c]	21 (100.0)	24 (100.0)	24 (100.0)	8 (88.9)	22 (100.0)	23 (100.0)	24 (100.0)	28 (100.0)	174 (99.4)
Received the additional booster vaccination	9 (42.9)	13 (54.2)	13 (54.2)	0	14 (63.6)	16 (69.6)	15 (62.5)	0	80 (45.7)
Completed the additional booster vaccination period[d]	9 (42.9)	13 (54.2)	12 (50.0)	0	14 (63.6)	16 (69.6)	15 (62.5)	0	79 (45.1)
Completed the 6-month post–additional booster vaccination visit	0	0	0	0	0	0	0	0	0
Completed the study	14 (66.7)	18 (75.0)	13 (54.2)	8 (88.9)	19 (86.4)	19 (82.6)	16 (66.7)	20 (71.4)	127 (72.6)
Withdrawn from the study	7 (33.3)	6 (25.0)	11 (45.8)	1 (11.1)	3 (13.6)	4 (17.4)	8 (33.3)	8 (28.6)	48 (27.4)
Withdrawn after the first booster vaccination and before the 1-month post–first booster vaccination visit	0	0	0	1 (11.1)	0	0	0	0	1 (0.6)
Withdrawn after the 1-month post–first booster vaccination visit and before the additional booster vaccination visit	6 (28.6)	6 (25.0)	9 (37.5)	0	3 (13.6)	2 (8.7)	6 (25.0)	8 (28.6)	40 (22.9)
Withdrawn after the additional booster vaccination visit	1 (4.8)	0	2 (8.3)	0	0	2 (8.7)	2 (8.3)	0	7 (4.0)
Reason for withdrawal									
Protocol deviation	4 (19.0)	5 (20.8)	4 (16.7)	0	0	2 (8.7)	2 (8.3)	4 (14.3)	21 (12.0)
No longer meets eligibility criteria	3 (14.3)	0	5 (20.8)	0	2 (9.1)	1 (4.3)	4 (16.7)	2 (7.1)	17 (9.7)
Withdrawal by subject	0	1 (4.2)	2 (8.3)	0	0	0	0	1 (3.6)	4 (2.3)
Lost to follow-up	0	0	0	1 (11.1)	0	0	1 (4.2)	0	2 (1.1)
Other	0	0	0	0	1 (4.5)	1 (4.3)	1 (4.2)	1 (3.6)	4 (2.3)

a. N = number of assigned subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. First booster vaccination period: from the first booster vaccination to the 1-month follow-up visit after the first booster vaccination.
d. Additional booster vaccination period: from the additional booster vaccination to the 1-month follow-up visit after the additional booster vaccination.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adds Table Generation: 19MAY2023 (04:24)
(Database Snapshot Date: 28APR2023) Output File: ./nda2 unblinded/C4591001 CSR/adds s002 p1 bd

Exposure

Participants who received the first and additional booster vaccinations of BNT162b2 (30 µg) are presented below.

Table 17: Vaccine Administration Timing – Phase 1 – Subjects Who Received Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Initial Vaccine Group (as Administered)							
	BNT162b1				BNT162b2			
	10µg n[a] (%)	20µg n[a] (%)	30µg n[a] (%)	100µg n[a] (%)	10µg n[a] (%)	20µg n[a] (%)	30µg n[a] (%)	Placebo n[a] (%)
First booster vaccination[b]								
N[c]	21	24	24	9	22	23	24	28
<9 Months	3 (14.3)	24 (100.0)	12 (50.0)	0	21 (95.5)	22 (95.7)	23 (95.8)	3 (10.7)
≥9-<12 Months	18 (85.7)	0	12 (50.0)	0	1 (4.5)	1 (4.3)	0	24 (85.7)
≥12-<15 Months	0	0	0	0	0	0	0	1 (3.6)
≥15-<18 Months	0	0	0	9 (100.0)	0	0	0	0
≥18-<21 Months	0	0	0	0	0	0	1 (4.2)	0
Mean (SD)	9.6 (0.67)	8.5 (0.28)	9.3 (0.60)	15.8 (0.63)	8.5 (0.56)	8.4 (0.18)	8.7 (2.21)	9.7 (0.82)
Median	10.0	8.5	9.2	15.5	8.4	8.4	8.3	9.4
Min, max	(8.8, 10.8)	(8.0, 8.8)	(8.5, 10.1)	(15.3, 17.3)	(7.8, 10.3)	(8.3, 9.0)	(7.9, 19.0)	(8.7, 12.3)
Additional booster vaccination[d]								
N[c]	9	13	13	0	14	16	15	0
<15 Months	4 (44.4)	7 (53.8)	3 (23.1)		4 (28.6)	0	1 (6.7)	
≥15-<18 Months	5 (55.6)	6 (46.2)	10 (76.9)		10 (71.4)	16 (100.0)	14 (93.3)	
Mean (SD)	15.1 (0.43)	15.0 (0.23)	15.3 (0.36)		15.4 (0.46)	15.4 (0.34)	15.5 (0.40)	
Median	15.0	14.9	15.3		15.6	15.6	15.7	
Min, max	(14.7, 15.9)	(14.7, 15.3)	(14.8, 15.8)		(14.8, 16.0)	(15.0, 15.9)	(14.8, 15.9)	

a. n = Number of subjects with the specified characteristic.
b. Months calculated since the second dose of BNT162b1/BNT162b2.
c. This value is the denominator for the percentage calculations of the subcategories.
d. Months calculated since the first booster dose of BNT162b2.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 05MAY2023 (01:26)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/advx_s002_p1_bd

Follow-up Time

Median follow-up time for participants that received the first booster vaccination to the end of the study ranged from 12.3 to 21.4 months and 5.3 to 6.4 months for the additional booster vaccination to the end of the study.

Table 18: Follow-up Time After Booster Dose – Phase 1 – Subjects Who Received Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Initial Vaccine Group (as Administered)							
	BNT162b1				BNT162b2			
	10µg n[a] (%)	20µg n[a] (%)	30µg n[a] (%)	100µg n[a] (%)	10µg n[a] (%)	20µg n[a] (%)	30µg n[a] (%)	Placebo n[a] (%)
Total exposure from the additional booster vaccination to the end of study								
Received the additional booster vaccination[b]	9	13	13	0	14	16	15	0
<3 Months	0	0	1 (7.7)		0	0	0	
≥3-<6 Months	9 (100.0)	13 (100.0)	12 (92.3)		1 (7.1)	1 (6.3)	1 (6.7)	
≥6 Months	0	0	0		13 (92.9)	15 (93.8)	14 (93.3)	
Mean (SD)	5.5 (0.29)	5.6 (0.25)	5.0 (1.22)		6.3 (0.34)	6.3 (0.25)	6.3 (0.41)	
Median	5.6	5.7	5.3		6.3	6.4	6.4	
Min, max	(5.0, 5.9)	(5.3, 6.0)	(1.1, 5.8)		(5.3, 6.7)	(5.6, 6.5)	(4.9, 6.5)	
Total exposure from the first booster vaccination to the end of study								
Received the first booster vaccination[b]	21	24	24	9	22	23	24	28
<12 Months	4 (19.0)	1 (4.2)	1 (4.2)	2 (22.2)	0	1 (4.3)	4 (16.7)	9 (32.1)
≥12-<15 Months	3 (14.3)	5 (20.8)	5 (20.8)	7 (77.8)	2 (9.1)	1 (4.3)	2 (8.3)	19 (67.9)
≥15-<18 Months	5 (23.8)	5 (20.8)	6 (25.0)	0	6 (27.3)	5 (21.7)	2 (8.3)	0
≥18-<21 Months	8 (38.1)	13 (54.2)	12 (50.0)	0	0	0	2 (8.3)	0
≥21 Months	1 (4.8)	0	0	0	14 (63.6)	16 (69.6)	14 (58.3)	0
Mean (SD)	16.7 (4.07)	18.1 (3.30)	17.7 (3.31)	11.1 (3.02)	19.8 (2.73)	19.7 (4.07)	18.4 (4.98)	11.1 (2.52)
Median	17.0	20.4	18.6	12.3	21.2	21.4	21.4	12.4
Min, max	(8.6, 21.5)	(9.9, 20.8)	(9.5, 20.8)	(3.3, 12.8)	(14.3, 22.3)	(4.1, 22.3)	(5.7, 22.3)	(6.0, 13.5)

a. n = Number of subjects with the specified characteristic.
b. This value is the denominator for the percentage calculations for the subcategories.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 19MAY2023 (02:57)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adsl_fup_p1_bd

Demographics

Demographic characteristics of participants in Phase 1 who received the first booster dose of BNT162b2 (30 µg) are shown below.

Table 19: Demographic Characteristics – Phase 1 – Subjects Who Received the First Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Initial Vaccine Group (as Administered)								
	BNT162b1				BNT162b2				
	10µg (N[a]=21) n[b] (%)	20µg (N[a]=24) n[b] (%)	30µg (N[a]=24) n[b] (%)	100µg (N[a]=9) n[b] (%)	10µg (N[a]=22) n[b] (%)	20µg (N[a]=23) n[b] (%)	30µg (N[a]=24) n[b] (%)	Placebo (N[a]=28) n[b] (%)	Total (N[a]=175) n[b] (%)
Sex									
Male	9 (42.9)	13 (54.2)	10 (41.7)	3 (33.3)	5 (22.7)	11 (47.8)	9 (37.5)	12 (42.9)	72 (41.1)
Female	12 (57.1)	11 (45.8)	14 (58.3)	6 (66.7)	17 (77.3)	12 (52.2)	15 (62.5)	16 (57.1)	103 (58.9)
Race									
White	17 (81.0)	22 (91.7)	20 (83.3)	8 (88.9)	21 (95.5)	21 (91.3)	21 (87.5)	28 (100.0)	158 (90.3)
Black or African American	1 (4.8)	2 (8.3)	0	0	0	2 (8.7)	1 (4.2)	0	6 (3.4)
Asian	3 (14.3)	0	4 (16.7)	1 (11.1)	1 (4.5)	0	2 (8.3)	0	11 (6.3)
Ethnicity									
Hispanic/Latino	1 (4.8)	0	1 (4.2)	0	0	0	0	0	2 (1.1)
Non-Hispanic/non-Latino	20 (95.2)	24 (100.0)	22 (91.7)	9 (100.0)	22 (100.0)	23 (100.0)	24 (100.0)	28 (100.0)	172 (98.3)
Not reported	0	0	1 (4.2)	0	0	0	0	0	1 (0.6)
Country									
USA	21 (100.0)	24 (100.0)	24 (100.0)	9 (100.0)	22 (100.0)	23 (100.0)	24 (100.0)	28 (100.0)	175 (100.0)
Age at booster vaccination (years)									
Mean (SD)	49.1 (20.89)	58.4 (14.95)	53.6 (18.71)	39.7 (10.48)	55.6 (16.99)	56.1 (18.26)	53.8 (17.33)	55.1 (17.82)	53.9 (17.73)
Median	42.0	60.5	59.0	37.0	66.0	65.0	60.0	60.5	54.0
Min, max	(25, 83)	(31, 82)	(24, 77)	(26, 54)	(22, 74)	(24, 82)	(24, 75)	(20, 78)	(20, 83)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 05MAY2023 (11:39)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adsl_s005_p1_d3

Assessor´s comment:

In this Phase 1 study, primary series of BNT162b1 (10, 20, 30, 100µg) and BNT162b2 (10, 20, 30 µg) was administered to subgroups including 24 adult subjects in each group (total n=195). Most of these subjects then received one booster dose of BNT162b2 (30 µg), and an additional booster dose was administered to about half of the study population. Median follow-up time since first booster dose was 12-21 months in the different initial vaccine groups, and the median follow-up time after the additional booster dose was 5-6 months.

A slightly higher frequency of female participants was noted (59% vs 41%), majority were white, and the study was executed in USA. The age of the subject ranged between 20-83 years.

7.1.2. Phase 2/3

Disposition of Participants from Dose 1 of BNT162b2 30 µg to Before Booster Dose

Final disposition of all randomised Phase 2/3 participants 12 through 15 years of age and ≥16 years of age is presented below for the blinded placebo-controlled and open-label follow-up periods.

The following is noted for these participants:

- Individuals 12 through 15 years of age and ≥ 16 years of age were unblinded as they became locally eligible and wished to know their vaccine assignment to confirm prior vaccination with BNT162b2 (if randomised to this group), or to receive BNT162b2 (if randomised to placebo). Unblinded recipients originally randomised to BNT162b2 were followed in an open-label manner. Unblinded recipients originally randomised to placebo were offered BNT162b2 vaccination (Doses 3 and 4 [first and second dose of BNT162b2 30 µg, respectively]) and were also followed in an open-label manner.
- Seventeen participants were inadvertently enrolled at multiple sites, and they were excluded from all data summaries.

Table 20: Disposition of All Randomised Subjects – From Dose 1 to Before Booster Dose – Phase 2/3 Subjects

	Vaccine Group (as Randomized)				
	12-15 Years		≥16 Years		
	BNT162b2 (30 µg) (N[a]=1134) n[b] (%)	Placebo (N[a]=1130) n[b] (%)	BNT162b2 (30 µg) (N[a]=22071) n[b] (%)	Placebo (N[a]=22071) n[b] (%)	Total (N[a]=46406) n[b] (%)
Randomized	1134 (100.0)	1130 (100.0)	22071 (100.0)	22071 (100.0)	46406 (100.0)
Not vaccinated	3 (0.3)	1 (0.1)	55 (0.2)	48 (0.2)	107 (0.2)
Original blinded, placebo-controlled follow-up period					
Vaccinated	1131 (99.7)	1129 (99.9)	22016 (99.8)	22021 (99.8)	46297 (99.8)
Dose 1	1131 (99.7)	1129 (99.9)	22016 (99.8)	22021 (99.8)	46297 (99.8)
Dose 2	1124 (99.1)	1119 (99.0)	21661 (98.1)	21641 (98.1)	45545 (98.1)
Discontinued from the original blinded, placebo-controlled vaccination period[c]	3 (0.3)	14 (1.2)	335 (1.5)	527 (2.4)	879 (1.9)
Reason for discontinuation					
Lost to follow-up	0	0	156 (0.7)	152 (0.7)	308 (0.7)
Withdrawal by subject	0	1 (0.1)	107 (0.5)	181 (0.8)	289 (0.6)
No longer meets eligibility criteria	0	7 (0.6)	14 (0.1)	121 (0.5)	142 (0.3)
Adverse event	1 (0.1)	0	22 (0.1)	25 (0.1)	48 (0.1)
Physician decision	1 (0.1)	0	5 (0.0)	8 (0.0)	14 (0.0)
Protocol deviation	0	2 (0.2)	3 (0.0)	8 (0.0)	13 (0.0)
Pregnancy	0	0	4 (0.0)	6 (0.0)	10 (0.0)
Death	0	0	3 (0.0)	4 (0.0)	7 (0.0)
Medication error without associated adverse event	0	0	3 (0.0)	1 (0.0)	4 (0.0)
Withdrawal by parent/guardian	0	1 (0.1)	1 (0.0)	0	2 (0.0)
Other	1 (0.1)	3 (0.3)	17 (0.1)	21 (0.1)	42 (0.1)
Unblinded before the 1-month post–Dose 2 visit	12 (1.1)	21 (1.9)	262 (1.2)	245 (1.1)	540 (1.2)
Completed the 1-month post–Dose 2 visit	1119 (98.7)	1105 (97.8)	21473 (97.3)	21423 (97.1)	45120 (97.2)
Completed the study	3 (0.3)	2 (0.2)	21 (0.1)	37 (0.2)	63 (0.1)
Withdrawn from the study	9 (0.8)	17 (1.5)	495 (2.2)	635 (2.9)	1156 (2.5)
Withdrawn after Dose 1 and before Dose 2	0	0	186 (0.8)	217 (1.0)	403 (0.9)
Withdrawn after Dose 2 and before the 1-month post–Dose 2 visit	0	3 (0.3)	103 (0.5)	145 (0.7)	251 (0.5)
Withdrawn after the 1-month post–Dose 2 visit	9 (0.8)	14 (1.2)	206 (0.9)	273 (1.2)	502 (1.1)
Reason for withdrawal from the study					
Lost to follow-up	4 (0.4)	2 (0.2)	256 (1.2)	281 (1.3)	543 (1.2)
Withdrawal by subject	1 (0.1)	7 (0.6)	139 (0.6)	250 (1.1)	397 (0.9)
Protocol deviation	0	0	15 (0.1)	39 (0.2)	54 (0.1)
No longer meets eligibility criteria	0	2 (0.2)	16 (0.1)	21 (0.1)	39 (0.1)
Death	0	0	18 (0.1)	16 (0.1)	34 (0.1)
Adverse event	0	0	9 (0.0)	9 (0.0)	18 (0.0)
Physician decision	0	0	5 (0.0)	7 (0.0)	12 (0.0)
Withdrawal by parent/guardian	1 (0.1)	5 (0.4)	1 (0.0)	0	7 (0.0)
Refused further study procedures	0	0	2 (0.0)	0	2 (0.0)
Pregnancy	0	0	0	1 (0.0)	1 (0.0)
Medication error without associated adverse event	0	0	1 (0.0)	0	1 (0.0)
Other	3 (0.3)	1 (0.1)	33 (0.1)	11 (0.0)	48 (0.1)
Open-label follow-up period					
Originally randomized to BNT162b2	1119 (98.7)		21500 (97.4)		
Received Dose 2/unplanned dose	4 (0.4)		139 (0.6)		
Completed the 1-month post–Dose 2 visit	12 (1.1)		233 (1.1)		
Withdrawn from the study	402 (35.4)		11764 (53.3)		
Withdrawn before the 6-month post–Dose 2 visit	31 (2.7)		402 (1.8)		
Withdrawn after the 6-month post–Dose 2 visit	371 (32.7)		11362 (51.5)		
Reason for withdrawal from the study					
No longer meets eligibility criteria	106 (9.3)		796 (3.6)		
Withdrawal by subject	41 (3.6)		730 (3.3)		
Lost to follow-up	30 (2.6)		623 (2.8)		
Protocol deviation	21 (1.9)		493 (2.2)		
Death	0		43 (0.2)		
Physician decision	0		27 (0.1)		
Withdrawal by parent/guardian	14 (1.2)		2 (0.0)		
Refused further study procedures	0		7 (0.0)		
Adverse event	0		4 (0.0)		
Pregnancy	0		1 (0.0)		
Other	190 (16.8)		9038 (40.9)		
Originally randomized to placebo		1110 (98.2)		21351 (96.7)	
Withdrawn from the study after unblinding and before receiving BNT162b2		81 (7.2)		871 (3.9)	
Received first dose of BNT162b2 [30 µg]		1014 (89.7)		20358 (92.2)	
Received second dose of BNT162b2 [30 µg]		1001 (88.6)		20280 (91.9)	
Discontinued from the open-label vaccination period[d]		13 (1.2)		168 (0.8)	
Reason for discontinuation from the open-label vaccination period					
Lost to follow-up		2 (0.2)		89 (0.4)	
Withdrawal by subject		2 (0.2)		31 (0.1)	
Protocol deviation		6 (0.5)		14 (0.1)	
No longer meets eligibility criteria		0		10 (0.0)	
Adverse event		0		6 (0.0)	
Death		0		3 (0.0)	
Physician decision		0		3 (0.0)	
Pregnancy		0		1 (0.0)	
Refused further study procedures		1 (0.1)		0	
Other		2 (0.2)		11 (0.0)	
Completed the 1-month post–second dose of BNT162b2 visit		1001 (88.6)		20162 (91.4)	
Withdrawn from the study		235 (20.8)		5158 (23.4)	
Withdrawn after first dose of BNT162b2 and before second dose of BNT162b2		10 (0.9)		72 (0.3)	
Withdrawn after second dose of BNT162b2 and before the 1-month post–second dose of BNT162b2 visit		3 (0.3)		96 (0.4)	
Withdrawn after the 1-month post–second dose of BNT162b2 visit		222 (19.6)		4990 (22.6)	
Reason for withdrawal from the study					
No longer meets eligibility criteria		96 (8.5)		1345 (6.1)	
Lost to follow-up		31 (2.7)		638 (2.9)	
Withdrawal by subject		23 (2.0)		535 (2.4)	
Protocol deviation		15 (1.3)		530 (2.4)	
Death		1 (0.1)		38 (0.2)	
Physician decision		0		20 (0.1)	
Refused further study procedures		0		5 (0.0)	
Adverse event		0		3 (0.0)	
Withdrawal by parent/guardian		3 (0.3)		0	
Pregnancy		0		1 (0.0)	
Other		66 (5.8)		2043 (9.3)	

Note: Human immunodeficiency virus (HIV)-positive subjects are included in this summary but analyzed and reported separately.
Note: Subjects randomized but did not sign informed consent or had a significant quality event due to lack of PI oversight are not included in any analysis population.
Note: Because of a dosing error, four subjects received an additional dose of BNT162b2 (30 µg) at an unscheduled visit after receiving 1 dose of BNT162b2 (30 µg) and 1 dose of placebo. Two subjects received an additional dose of BNT162b2 (30 µg) at an unscheduled visit after receiving 2 doses of BNT162b2 (30 µg).
a. N = number of randomized subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Original blinded, placebo-controlled vaccination period: from Dose 1 to the 1-month post–Dose 2 visit. Subjects who missed the 1-month post–Dose 2 visit but completed subsequent visits were considered as completed vaccination period as well.
d. Open-label vaccination period: from first dose of BNT162b2 [30 µg] to the 1-month post–second dose of BNT162b2 [30 µg] visit. Subjects who missed the 1-month post–second dose of BNT162b2 [30 µg] visit but completed subsequent visits were considered as completed open-label vaccination period as well.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adds Table Generation: 12MAY2023 (02:17)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adds_s002_p23

Participants With Confirmed Stable HIV Disease

In total 201 HIV-positive subjects were randomised and vaccinated (n=100 BNT162b2; n=101 Placebo). During the blinded placebo-controlled follow-up period, most HIV-positive participants randomised to the BNT162b2 and placebo groups received Doses 1 and 2. There were 4 participants (4.0%) in the BNT162b2 group and 4 participants (4.0%) in the placebo group who discontinued from the vaccination period (Dose 1 to 1 month after Dose 2). Most participants completed the 1-month post–Dose 2 visit (≥97.0%). Few participants in the BNT162b2 and placebo groups were withdrawn from the study (2.0% and 4.0%, respectively). The reasons were withdrawal by the participant, lost to follow-up, and death.
In the BNT162b2 (30 µg) group, during the open-label follow-up period, there were 58 participants (58.0%) withdrawn from the study, and most were due to other reasons. In the placebo group, during the open-label follow-up period, most participants originally randomised to placebo received Doses 1 and 2 (89.1% and 88.1%, respectively) of BNT162b2. There were 19 participants (18.8%) in this group who were withdrawn from the study. The most common reason was "other".

Assessor´s comment:

The final disposition for all randomised subjects to the Phase 2/3 study C4591001 included a total of 46406 subjects aged ≥12 years, of which 99.8% received the two doses included in the primary series of BNT162b2 30µg. Among the subjects who were originally randomised to placebo 89-92% received two doses of BNT162b2 30µg. In total were 1156 subjects withdrawn from the study, most of them due to lost to follow-up (n=543) or withdrawn by subject (n=397).

In total were 201 HIV-positive subjects were randomised and vaccinated (n=100 BNT162b2; n=101 Placebo). Most of them received the primary series and remained in the study. In the placebo group who later received BNT162b2 30µg, it in noted that 19 participants (19%) of the participants withdrawn due to "other reason".

Disposition of Participants who Received Booster Dose of BNT162b2 30 µg.

Participants who Received Booster Dose of BNT162b2 30 µg as Part of Protocol Amendment 18

The final disposition of Phase 2/3 participants 12 through 15 years of age and ≥16 years of age who received 2 doses of BNT162b2 30 µg and then received a booster dose of BNT162b2 30 µg as part of protocol amendment 18 is presented below.

Table 21: Disposition of Subjects – Phase 2/3 – Subjects Who Received Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 18

	Vaccine Group (as Assigned)		
	BNT162b2 (30 µg)		
	12-15 Years (N^a=825) n^b (%)	≥16 Years (N^a=22581) n^b (%)	Total (N^a=23406) n^b (%)
Received the booster vaccination	825 (100.0)	22581 (100.0)	23406 (100.0)
Completed the booster vaccination period[c]	819 (99.3)	22430 (99.3)	23249 (99.3)
Completed the 6-month post–booster vaccination visit	677 (82.1)	20241 (89.6)	20918 (89.4)
Completed the study	649 (78.7)	14990 (66.4)	15639 (66.8)
Withdrawn from the study	176 (21.3)	7591 (33.6)	7767 (33.2)
Withdrawn after the booster vaccination and before the 1-month post–booster vaccination visit	5 (0.6)	146 (0.6)	151 (0.6)
Withdrawn after the 1-month and before the 6-month post–booster vaccination visit	95 (11.5)	1967 (8.7)	2062 (8.8)
Withdrawn after the 6-month post–booster vaccination visit	76 (9.2)	5478 (24.3)	5554 (23.7)
Reason for withdrawal			
Protocol deviation	20 (2.4)	2356 (10.4)	2376 (10.2)
Withdrawal by subject	6 (0.7)	1653 (7.3)	1659 (7.1)
Lost to follow-up	25 (3.0)	1043 (4.6)	1068 (4.6)
No longer meets eligibility criteria	0	252 (1.1)	252 (1.1)
Death	0	47 (0.2)	47 (0.2)
Physician decision	0	14 (0.1)	14 (0.1)
Refused further study procedures	0	3 (0.0)	3 (0.0)
Withdrawal by parent/guardian	1 (0.1)	2 (0.0)	3 (0.0)
Other	124 (15.0)	2221 (9.8)	2345 (10.0)

Note: Human immunodeficiency virus (HIV)-positive subjects are included in this summary but analyzed and reported separately.
a. N = number of assigned subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Booster vaccination period: from booster vaccination to the 1-month follow-up visit after the booster vaccination.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adds Table Generation: 19MAY2023 (02:13)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adds_s002_p23_d3

Among the 99 HIV-positive participants who received a booster dose of BNT162b2 in Phase 2/3, 98 (99.0%) completed the booster vaccination period from the third dose of BNT162b2 to the 1-month follow-up visit, and 78 participants (78.8%) completed the study. After receiving the booster dose, 21 participants (21.2%) were withdrawn from the study mostly due to other reasons or protocol deviations.

Protocol amendment 18 is illustrated below:

Document	Version Date	Summary and Rationale for Changes

Protocol amendment 18	07 September 2021	• Addition of procedures for monitoring potential myocarditis or pericarditis.
		• Addition of a third dose of BNT162b2 for participants who meet specified recommendations and have not yet received a third dose.
		  • Added corresponding objectives, estimands, and endpoints.
		  • Added corresponding SoA and procedures.
		  • Added details in the statistical methods sections.
		• Added the instruction that participants who receive COVID-19 vaccines outside of the study from protocol amendment 18 onwards should be withdrawn.

Assessor´s comment:

A total number of 23,406 participants in the Phase 2/3 study received a first booster dose, and 89% of them had completed the 6-month post-booster vaccination visit. The addition of a booster dose was described in protocol amendment 18.

BNT162b2-Naïve Participants Assigned to Receive BNT162b2$_{SA}$ and Received Booster Dose of BNT162b2 30 µg as Part of Protocol Amendment 18

The final disposition of all randomised Phase 3 BNT162b2-naïve participants assigned to receive BNT162b2SA is presented below. These participants were rerandomised to receive 1 or 2 booster doses of BNT162b2 or BNT162b2$_{SA}$ (encoding the P2 S containing South Africa B.1.351 variant–specific mutations).

Table 22: Disposition of Subjects – Phase 3 – BNT162b2-Naïve Subjects Assigned to Receive BNT162b2SA

	Vaccine Group (as Assigned)
	BNT162b2$_{SA}$ (30 µg) (N[a]=333) n[b] (%)
Assigned	333 (100.0)
Not vaccinated	3 (0.9)
Received Dose 1	330 (99.1)
Received Dose 2	329 (98.8)
Completed the vaccination period[c]	321 (96.4)
Completed the 6-month post–Dose 2 visit	278 (83.5)
Received the booster vaccination	242 (72.7)
Completed the booster vaccination period[d]	237 (71.2)
Completed the 6-month post–booster vaccination visit	221 (66.4)
Completed the study	228 (68.5)
Withdrawn from the study	102 (30.6)
Withdrawn after Dose 1 and before Dose 2	1 (0.3)
Withdrawn after Dose 2 and before the 1-month post–Dose 2 visit	8 (2.4)
Withdrawn after the 1-month post–Dose 2 visit and before the 6-month post–Dose 2 visit	20 (6.0)
Withdrawn after the 6-month post–Dose 2 visit and before the booster vaccination	31 (9.3)
Withdrawn after the booster vaccination and before the 1-month post–booster vaccination visit	5 (1.5)
Withdrawn after the 1-month post–booster vaccination visit and before the 6-month post–booster vaccination visit	12 (3.6)
Withdrawn after the 6-month post–booster vaccination visit	25 (7.5)
Reason for withdrawal	
Lost to follow-up	50 (15.0)
Withdrawal by subject	18 (5.4)
No longer meets eligibility criteria	8 (2.4)
Protocol deviation	2 (0.6)
Other	24 (7.2)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of assigned subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Vaccination period: from Dose 1 to the 1-month post–Dose 2 visit.
d. Booster vaccination period: from booster vaccination to the 1-month follow-up visit after the booster vaccination.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adds Table Generation: 12MAY2023 (03:39)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adds_s002_na

Assessor´s comment:

Among the 333 included BNT162b2-naïve subjects, 330 received a dose of the variant vaccine BNT162b2$_{SA}$ (South Africa B.1.351). The 6-month post-booster dose vaccination visit was completed by 66% of the subjects. Withdrawn was reported among 25 (7,5%) of the subjects.

BNT162b2-Experienced Participants Who Were Rerandomised to Receive Booster Dose(s) Under Protocol Amendments 14 and 15 and Received an Additional Booster Dose of BNT162b2 (30 µg)

The final disposition of Phase 2/3 BNT162b2-experienced participants who received the 2-dose primary series of BNT162b2 30 µg and were rerandomised/assigned to receive a booster (Dose 3) of BNT162b2 (30 µg, or lower dose of 5 or 10 µg), or 1 or 2 booster doses of BNT162b2$_{SA}$ 30 µg under protocol amendments 14 and 15, is presented below.

Table 23: Disposition of Subjects – Phase 2/3 – BNT162b2-Experienced Subjects Who Were Rerandomised/Assigned to Receive Booster Dose(s) – Booster Safety Population

	Booster Vaccine Group (as Rerandomized)				Booster Vaccine Group (as Assigned)
	BNT162b2 (30 µg) (N[a]=312) n[b] (%)	BNT162b2$_{SA}$ (30 µg) (N[a]=313) n[b] (%)	BNT162b2 (5 µg) (N[a]=79) n[b] (%)	BNT162b2 (10 µg) (N[a]=76) n[b] (%)	BNT162b2$_{SA}$ (30 µg, 2 Doses) (N[a]=30) n[b] (%)
Rerandomized/assigned	312 (100.0)	313 (100.0)	79 (100.0)	76 (100.0)	30 (100.0)
Did not receive the first booster vaccination	0	0	0	0	0
Did not receive the second booster vaccination					2 (6.7)
Did not receive the additional booster vaccination	128 (41.0)	116 (37.1)	46 (58.2)	38 (50.0)	15 (50.0)
Received the first booster vaccination	312 (100.0)	313 (100.0)	79 (100.0)	76 (100.0)	30 (100.0)
Completed the first booster vaccination period[c]	309 (99.0)	311 (99.4)	79 (100.0)	76 (100.0)	27 (90.0)
Completed the 6-month post–first booster vaccination visit	298 (95.5)	303 (96.8)	78 (98.7)	75 (98.7)	28 (93.3)
Received the additional booster vaccination	184 (59.0)	197 (62.9)	33 (41.8)	38 (50.0)	15 (50.0)
Completed the additional booster vaccination period[d]	183 (58.7)	190 (60.7)	33 (41.8)	38 (50.0)	15 (50.0)
Completed the 6-month post–additional booster vaccination visit	0	0	1 (1.3)	0	0
Completed the study	253 (81.1)	249 (79.6)	45 (57.0)	43 (56.6)	22 (73.3)
Withdrawn from the study	59 (18.9)	64 (20.4)	34 (43.0)	33 (43.4)	8 (26.7)
Withdrawn after the first booster vaccination and before the 1-month post–first/second[e] booster vaccination visit	3 (1.0)	2 (0.6)	0	0	1 (3.3)
Withdrawn after the 1-month post–first/second[e] booster vaccination visit and before the 6-month post–first booster vaccination visit	10 (3.2)	8 (2.6)	1 (1.3)	1 (1.3)	1 (3.3)
Withdrawn after the 6-month post–first booster vaccination visit and before the additional booster vaccination visit	36 (11.5)	38 (12.1)	33 (41.8)	31 (40.8)	5 (16.7)
Withdrawn after additional booster vaccination visit	10 (3.2)	16 (5.1)	0	1 (1.3)	1 (3.3)
Reason for withdrawal					
Withdrawal by subject	18 (5.8)	14 (4.5)	11 (13.9)	12 (15.8)	4 (13.3)
No longer meets eligibility criteria	10 (3.2)	9 (2.9)	17 (21.5)	19 (25.0)	0
Lost to follow-up	16 (5.1)	24 (7.7)	1 (1.3)	0	3 (10.0)
Protocol deviation	11 (3.5)	12 (3.8)	3 (3.8)	2 (2.6)	0
Physician decision	0	2 (0.6)	0	0	0
Other	4 (1.3)	3 (1.0)	2 (2.5)	0	1 (3.3)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of assigned subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. The first booster vaccination period: from the first booster vaccination to the 1-month follow-up visit after the first/second booster vaccination.
d. The additional booster vaccination period: from the additional booster vaccination to the 1-month follow-up visit after the additional booster vaccination(s).
e. The second booster vaccination is applicable to subjects who received 2 doses of BNT162b2$_{SA}$ (30 µg, 2 doses) during the first booster vaccination period.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adds Table Generation: 05MAY2023 (01:28)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adds_s002_p3_d4

Main updates included in protocol amendment 14 (02 March 2021)

Protocol amendment 14	02 March 2021	• In order to further describe duration of protection, and heterologous/homologous protection against the emerging VOCs, an additional dose of BNT162b2 or BNT162b2$_{SA}$ will be given to approximately 600 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2; a further dose of BNT162b2$_{SA}$ will be given to approximately 30 of those participants who receive BNT162b2$_{SA}$:
		  ◦ Added corresponding objectives, estimands, and endpoints
		  ◦ Added corresponding SoA and procedures
		  ◦ Added details in the statistical methods sections.
		• Approximately 300 BNT162b2-naïve participants will be enrolled and receive 2 doses of BNT162b2$_{SA}$ to describe heterologous/homologous protection against the emerging VOCs and reference strains:
		  ◦ Added corresponding objectives, estimands, and endpoints
		  ◦ Added corresponding SoA and procedures
		  ◦ Added details in the statistical methods sections.

Protocol amendment 15 (25 March 2021)

Protocol amendment 15	25 March 2021	• In order to further characterize booster responses induced by BNT162b2, 2 additional lower-dose booster groups have been added to the subset for evaluation of boostability and protection against emerging VOCs. An additional 5-µg or 10-µg dose of BNT162b2 will be given to approximately 144 Phase 3 participants approximately 5 to 7 months after their second dose of BNT162b2. • To further describe cell-mediated immune responses following isolations of PBMCs in a subset of both the Phase 3 participants who receive a single booster vaccination and the BNT162b2-naïve group who receive BNT162b2$_{SA}$, additional genetic testing may also be performed; corresponding details and an appendix have been added. • An exploratory objective was added for Phase 3 participants to describe the immune response to a third dose of BNT162b2 or a third or fourth dose of BNT162b2$_{SA}$ at later time points to align with analyses and corresponding changes detailed in the statistical section. • Removed the lower age limit for eligibility for administration of BNT162b2 to those originally assigned to placebo: this will now be covered in the recommendations detailed separately, and available in the electronic study reference portal. • Allowed administration of BNT162b2 at Visits 101 and 102 to pregnant participants in certain circumstances. • To align with contraception requirements, reduced the EDP reporting period to 28 days after the last dose of study intervention.

Protocol amendment 19 (21 March 2022)

Protocol amendment 19	21 March 2022	• Inclusion of an additional 30-µg dose of BNT162b2 for eligible participants from protocol amendments 13-15 who received at least 3 doses of BNT162 in the study.
		  ◦ Added corresponding objectives, estimands, and endpoints.
		  ◦ Added corresponding SoA and procedures.
		  ◦ Added details in the statistical methods sections.
		• Added language to permit early discontinuation of participants for reasons including but not limited to the increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial.
		• Updated the eligibility window for participants to receive the third (booster) dose under protocol amendment 18 from at least 6 months after Dose 2 to at least 3 months after Dose 2 to provide maximum opportunity to all participants to receive the third dose.
		• Updated the existing objectives, estimands, and endpoints in line with the revised schedule and study duration, and where applicable, removed what is no longer relevant.
		• Clarified AE/SAE collection requirements for participants enrolled under protocol amendments 18 and 19.
		• Updated risk assessment as BNT162b2 is no longer a novel vaccine and there are extensive data available from both clinical trial and real-world settings.

Assessor´s comment:

In this part of the study (described in protocol amendment 14 and 15), subjects that had already received the primary series of BNT162b2 30 µg were rerandomised to receive booster doses of BNT162b2 at 5, 10, 30 µg or BNT162b2$_{SA}$ (N=780). In addition, 30 subjects were assigned to receive booster doses of BNT162b2$_{SA}$. All subjects received the first booster dose. The second booster dose was not received by 41% of the subjects in the BNT162b2 30 µg group. In the other groups 37-58% of the subjects did not receive the additional booster vaccination.

Exposure and Follow-up Time

Participants who Received Booster Dose of BNT162b2 30 µg as Part of Protocol Amendment 18

Participants 12 through 15 years of age, the median (min, max) time between Dose 2 and booster vaccination was 11.2 (6.3, 20.1) months. Most participants (93.9%) received the booster dose of BNT162b2 <15 months after Dose 2.

Participants 16 years of ag and older, the median (min, max) time between Dose 2 and booster vaccination was 10.1 (4.8, 22.7) months. Most participants (85.7%) received the booster dose of BNT162b2 <15 months after Dose 2.

Table 24: Vaccine Administration Timing – Phase 2/3 – Subjects Who Received Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 18

	Vaccine Group (as Assigned)	
	BNT162b2 (30 µg)	
	12-15 Years (N[a]=825) n[b] (%)	≥16 Years (N[a]=22581) n[b] (%)
Assigned	825 (100.0)	22581 (100.0)
Booster vaccination[c]	825 (100.0)	22581 (100.0)
<6 Months	0	27 (0.1)
≥6-<9 Months	372 (45.1)	6481 (28.7)
≥9-<12 Months	46 (5.6)	7926 (35.1)
≥12-<15 Months	357 (43.3)	4918 (21.8)
≥15-<18 Months	43 (5.2)	3091 (13.7)
≥18 Months	7 (0.8)	136 (0.6)
Mean (SD)	10.8 (2.94)	11.2 (2.85)
Median	11.2	10.1
Min, max	(6.3, 20.1)	(4.8, 22.7)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Months calculated since second dose of BNT162b2.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 05MAY2023 (01:26)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/advx_s002_p23_d3

Overall, median (min, max) follow-up time after booster vaccination was 9.5 (1.5, 10.7) months and 12.3 (0.0, 15.3) months for participants 12 through 15 years of age and ≥16 years of age, respectively.

Table 25: Follow-up Time After Booster Dose – Phase 2/3 – Subjects Who Received Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 18

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg)	
	12-15 Years (N[a]=825) n[b] (%)	≥16 Years (N[a]=22581) n[b] (%)
Total exposure from the booster vaccination to the end of study		
<6 Months	108 (13.1)	1227 (5.4)
≥6-<9 Months	185 (22.4)	4006 (17.7)
≥9-<12 Months	532 (64.5)	4429 (19.6)
≥12-<15 Months	0	12901 (57.1)
≥15 Months	0	18 (0.1)
Mean (SD)	8.7 (1.70)	10.9 (2.63)
Median	9.5	12.3
Min, max	(1.5, 10.7)	(0.0, 15.3)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 21MAY2023 (22:41)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adsl_fup_p23_d3

Assessor´s comment

Among the 22581 subjects ≥16 years of age that receive a booster vaccination, most of these vaccinations occurred 6-15 months after Dose 2. The median follow-up time after booster dose was 12.3 months.

BNT162b2-Naïve Participants Assigned to Receive BNT162b2$_{SA}$ and Received Booster Dose of BNT162b2 30 µg as Part of Protocol Amendment 18

The median (min, max) time between Dose 2 and booster vaccination was 6.6 (6.1, 14.1) months. Most participants (83.9%) received the booster dose of BNT162b2 <9 months after Dose 2.

Table 26: Vaccine Administration Timing – Phase 3 – BNT162b2-Naïve Subjects Assigned to Receive BNT162b2SA Who Received Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Assigned)
	BNT162b2 (30 µg) (N[a]=242) n[b] (%)
Assigned	242 (100.0)
Booster vaccination[c]	242 (100.0)
≥6-<9 Months	203 (83.9)
≥9-<12 Months	34 (14.0)
≥12-<15 Months	5 (2.1)
Mean (SD)	7.3 (1.52)
Median	6.6
Min, max	(6.1, 14.1)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Months calculated since second dose of BNT162b2.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 05MAY2023 (01:26)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/advx_s002_na_d3

Overall, median (min, max) follow-up time after study vaccination was 12.3 (2.6, 14.6) months.

Table 27: Follow-up Time After Booster Dose – Phase 3 – BNT162b2-Naïve Subjects Assigned to Receive BNT162b2SA Who Received Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Administered)
	BNT162b2 (30 µg) (N[a]=242) n[b] (%)
Total exposure from the booster vaccination to the end of study	
<9 Months	35 (14.5)
≥9-<12 Months	67 (27.7)
≥12-<15 Months	140 (57.9)
Mean (SD)	11.5 (2.22)
Median	12.3
Min, max	(2.6, 14.6)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 21MAY2023 (22:43)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adsl_fup_na_d3

Assessor´s comment:

Among the 242 BNT162b2-naïve subjects who received a booster dose of BNT162b2$_{SA}$, most of the booster vaccinations occurred 6-9 months after Dose 2. The median follow-up time was 12.3 months.

Phase 3 – BNT162b2-Experienced Subjects who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose)

The median time (min, max) between Dose 2 and booster vaccination ranged from 6.8 (5.6, 7.4) to 7.2 (5.6, 7.5) months.

Table 28: Vaccine Administration Timing – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose)

	Vaccine Group (as Randomized)			
	BNT162b2 (5 µg)		BNT162b2 (10 µg)	
	18-55 Years (N[a]=26) n[b] (%)	>55 Years (N[a]=53) n[b] (%)	18-55 Years (N[a]=25) n[b] (%)	>55 Years (N[a]=51) n[b] (%)
Rerandomized	26 (100.0)	53 (100.0)	25 (100.0)	51 (100.0)
Did not receive booster vaccination	0	0	0	0
Booster vaccination[c]	26 (100.0)	53 (100.0)	25 (100.0)	51 (100.0)
≥5-<6 Months	8 (30.8)	8 (15.1)	8 (32.0)	7 (13.7)
≥6-<7 Months	10 (38.5)	17 (32.1)	7 (28.0)	12 (23.5)
≥7 Months	8 (30.8)	28 (52.8)	10 (40.0)	32 (62.7)
Mean (SD)	6.6 (0.65)	6.8 (0.61)	6.6 (0.70)	6.9 (0.57)
Median	6.8	7.0	6.9	7.2
Min, max	(5.6, 7.4)	(5.7, 7.5)	(5.5, 7.5)	(5.6, 7.5)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Months calculated since Dose 2.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 28JUN2023 (00:21)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_G4_6MPD_CSR/advx_s002_time_g4_6m

The median (min, max) follow-up time since Dose 2 was 20.1 (15.0, 26.8) and 19.8 (13.3, 26.8) months for participants in the BNT162b2 (5 µg) 18 through 55 and >55 years of age groups, respectively, and 20.5 (14.3, 25.9) and 20.1 (12.4, 26.7) months for participants in the BNT162b2 (10 µg) 18 through 55 and >55 years of age groups, respectively.

Table 29: Follow-up Time After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose)

	Vaccine Group (as Administered)			
	BNT162b2 (5 µg)		BNT162b2 (10 µg)	
	18-55 Years (N^a=26) n^b (%)	>55 Years (N^a=53) n^b (%)	18-55 Years (N^a=25) n^b (%)	>55 Years (N^a=51) n^b (%)
Total exposure from booster vaccination to before additional booster dose				
<6 Months	0	1 (1.9)	0	0
≥6-<8 Months	0	1 (1.9)	0	6 (11.8)
≥8-<10 Months	5 (19.2)	8 (15.1)	5 (20.0)	6 (11.8)
≥10-<12 Months	1 (3.8)	6 (11.3)	3 (12.0)	1 (2.0)
≥12 Months	20 (76.9)	37 (69.8)	17 (68.0)	38 (74.5)
Mean (SD)	13.6 (3.29)	13.0 (3.34)	13.0 (2.73)	12.4 (3.00)
Median	13.3	13.1	13.6	13.1
Min, max	(8.7, 19.6)	(5.9, 19.9)	(8.8, 19.9)	(6.1, 19.2)
Total exposure from Dose 2 to before additional booster dose				
≥12-<14 Months	0	1 (1.9)	0	3 (5.9)
≥14-<16 Months	4 (15.4)	3 (5.7)	3 (12.0)	5 (9.8)
≥16-<18 Months	2 (7.7)	11 (20.8)	4 (16.0)	4 (7.8)
≥18-<20 Months	5 (19.2)	13 (24.5)	5 (20.0)	13 (25.5)
≥20 Months	15 (57.7)	25 (47.2)	13 (52.0)	26 (51.0)
Mean (SD)	20.2 (3.43)	19.7 (3.20)	19.6 (2.84)	19.3 (3.00)
Median	20.1	19.8	20.5	20.1
Min, max	(15.0, 26.8)	(13.3, 26.8)	(14.3, 25.9)	(12.4, 26.7)

Note: End of study date is used to calculate follow-up time when subject did not receive additional booster dose.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 29JUN2023 (01:22)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_G4_6MPD_CSR/adsl_fu_g4_6m

Assessor´s comment:

Among the 155 subjects that all received a low dose booster of BNT162b2 at either 5 or 10µg, all of them were administered at least five months after Dose 2. Median follow-up time were 19.8-20.1 months.

Phase 3 BNT162b2 Experienced Subjects who were Previously Rerandomised/Assigned to Receive Booster Dose(s) and Received an Additional Booster Dose of BNT162b2 (30µg) as Part of Protocol Amendment 19

All BNT162b2-experienced participants who were previously rerandomised/assigned to receive booster dose(s) and received an additional booster vaccination of BNT162b2 (30 µg) as part of protocol amendment 19, received the additional booster of BNT162b2 (30 µg), as assigned.

Table 30: Vaccine Administration Timing – Phase 3 – BNT162b2-Experienced Subjects Who Were Previously Rerandomised/Assigned to Receive Booster Dose(s), and Received an Additional Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 19 – Booster Safety Population

	Previous Booster Vaccine Group (as Administered)				
	BNT162b2 (30 µg) (N[a]=182) n[b] (%)	BNT162b2$_{5A}$ (30 µg) (N[a]=199) n[b] (%)	BNT162b2 (5 µg) (N[a]=33) n[b] (%)	BNT162b2 (10 µg) (N[a]=38) n[b] (%)	BNT162b2$_{5A}$ (30 µg, 2 Doses) (N[a]=15) n[b] (%)
Additional booster dose[c]	182 (100.0)	199 (100.0)	33 (100.0)	38 (100.0)	15 (100.0)
≥12-<14 Months	37 (20.3)	54 (27.1)	29 (87.9)	34 (89.5)	15 (100.0)
≥14-<16 Months	145 (79.7)	145 (72.9)	4 (12.1)	4 (10.5)	0
Mean (SD)	14.3 (0.40)	14.3 (0.40)	13.4 (0.37)	13.5 (0.36)	13.3 (0.29)
Median	14.3	14.3	13.3	13.3	13.3
Min, max	(13.5, 15.2)	(13.5, 15.1)	(12.9, 14.5)	(12.9, 14.4)	(12.9, 13.8)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Months calculated since the first/second booster dose, the second booster vaccination is applicable to subjects who received 2 doses of
BNT162b2$_{5A}$ (30 µg, 2 doses) during the first booster vaccination period.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 05MAY2023 (01:26)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/advx_s002_p3_d4

Participants that were rerandomised/assigned to receive booster vaccinations under protocol amendments 14 and 15 and received an additional booster dose of BNT162b2 (30 µg) as part of protocol amendment 19, had a median (min, max) follow-up time of 6.0 (0.9, 8.0) to 6.1 (4.8, 7.1) months from the additional booster dose to the end of the study. The median (min, max) follow-up time since the first/second booster dose was 19.1 (18.6, 20.5) to 20.1 (16.3, 21.8) months.

Table 31: Follow-up Time After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Previously Rerandomised/Assigned to Receive Booster Dose(s), and Received an Additional Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 19 – Booster Safety Population

	Previous Booster Vaccine Group (as Administered)				
	BNT162b2 (30 µg) (N[a]=182) n[b] (%)	BNT162b2$_{SA}$ (30 µg) (N[a]=199) n[b] (%)	BNT162b2 (5 µg) (N[a]=33) n[b] (%)	BNT162b2 (10 µg) (N[a]=38) n[b] (%)	BNT162b2$_{SA}$ (30 µg, 2 Doses) (N[a]=15) n[b] (%)
Total exposure from the additional booster dose to the end of study					
<3 Months	3 (1.6)	8 (4.0)	0	0	0
≥3-<6 Months	91 (50.0)	94 (47.2)	10 (30.3)	17 (44.7)	10 (66.7)
≥6-<9 Months	88 (48.4)	97 (48.7)	23 (69.7)	21 (55.3)	5 (33.3)
Mean (SD)	5.9 (0.69)	5.8 (0.97)	6.1 (0.44)	6.0 (0.49)	6.0 (0.56)
Median	6.0	6.0	6.1	6.0	5.9
Min, max	(1.7, 7.3)	(0.9, 8.0)	(4.8, 7.1)	(4.9, 7.0)	(5.4, 7.3)
Total exposure from the first/second[c] booster dose to the end of study					
≥15-<18 Months	3 (1.6)	9 (4.5)	0	0	0
≥18-<21 Months	143 (78.6)	153 (76.9)	33 (100.0)	38 (100.0)	15 (100.0)
≥21 Months	36 (19.8)	37 (18.6)	0	0	0
Mean (SD)	20.2 (0.72)	20.1 (1.00)	19.5 (0.41)	19.4 (0.41)	19.4 (0.64)
Median	20.1	20.0	19.5	19.5	19.1
Min, max	(16.3, 21.8)	(15.3, 21.9)	(18.8, 20.5)	(18.2, 20.3)	(18.6, 20.5)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. The second booster vaccination is applicable to subjects who received 2 doses of BNT162b2$_{SA}$ (30 µg, 2 doses) during the first booster vaccination period.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 05MAY2023 (01:26)
(Database Snapshot Date: 28APR2023) Output File: ./nda2 unblinded/C4591001 CSR/adsl fup p3 d4

Assessor´s comment:

Most of the subjects (N=467) that actually received a second booster dose (protocol amendment 14, 15 and 19) of either BNT162b2 at 5, 10, 30 µg or BNT162b2$_{SA}$ 30 µg, received their additional booster dose 12-16 months after the first booster dose. The medial follow-up time was 19.1-20.1 months.

Demographics

Phase 2/3 – Subjects Who Received Booster Dose of BNT162b2 (30µg) as Part of Protocol Amendment 18

Table 32: Demographic Characteristics – Phase 2/3 – Subjects Who Received Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 18 – Booster Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg)		
	12-15 Years (N[a]=825) n[b] (%)	≥16 Years (N[a]=22568) n[b] (%)	Total (N[a]=23393) n[b] (%)
Sex			
Male	407 (49.3)	11328 (50.2)	11735 (50.2)
Female	418 (50.7)	11240 (49.8)	11658 (49.8)
Race			
White	689 (83.5)	18905 (83.8)	19594 (83.8)
Black or African American	38 (4.6)	2020 (9.0)	2058 (8.8)
American Indian or Alaska Native	3 (0.4)	164 (0.7)	167 (0.7)
Asian	62 (7.5)	815 (3.6)	877 (3.7)
Native Hawaiian or other Pacific Islander	1 (0.1)	32 (0.1)	33 (0.1)
Multiracial	26 (3.2)	554 (2.5)	580 (2.5)
Not reported	6 (0.7)	78 (0.3)	84 (0.4)
Racial designation			
Japanese	3 (0.4)	72 (0.3)	75 (0.3)
Ethnicity			
Hispanic/Latino	89 (10.8)	7507 (33.3)	7596 (32.5)
Non-Hispanic/non-Latino	734 (89.0)	14979 (66.4)	15713 (67.2)
Not reported	2 (0.2)	82 (0.4)	84 (0.4)
Country			
Argentina	0	5195 (23.0)	5195 (22.2)
Brazil	0	1329 (5.9)	1329 (5.7)
Germany	0	336 (1.5)	336 (1.4)
South Africa	0	325 (1.4)	325 (1.4)
Turkey	0	244 (1.1)	244 (1.0)
USA	825 (100.0)	15139 (67.1)	15964 (68.2)
Age group (at booster vaccination)			
12-15 Years	825 (100.0)	0	825 (3.5)
16-55 Years	0	12902 (57.2)	12902 (55.2)
>55 Years	0	9666 (42.8)	9666 (41.3)
Age at booster vaccination (years)			
Mean (SD)	14.1 (0.80)	50.1 (16.60)	48.8 (17.60)
Median	14.0	52.0	51.0
Min, max	(13, 15)	(16, 92)	(13, 92)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)		361 (1.6)	361 (1.5)
Normal weight (≥18.5-24.9 kg/m^2)		6765 (30.0)	6765 (28.9)
Overweight (≥25.0-29.9 kg/m^2)		7739 (34.3)	7739 (33.1)
Obese (≥30.0 kg/m^2)		7696 (34.1)	7696 (32.9)
Missing		7 (0.0)	7 (0.0)
Body mass index (BMI) 12-15 years of age/obese[c]			
Yes	100 (12.1)		100 (0.4)
No	725 (87.9)		725 (3.1)

Note: Human immunodeficiency virus (HIV)-positive subjects are included in this summary but analyzed and reported separately.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Obese is defined as BMI ≥95th percentile from the growth chart. The obese status is based on data collected at Visit 1. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 05MAY2023 (11:39)
(Database Snapshot Date: 28APR2023) Output File: /nda2_unblinded/C4591001_CSR/adsl_s005_p23_d3

Assessor´s comment

The distribution between gender was 49% male and 51% female, most of the subjects where from the USA. The age ranged from 13-92 years, with a median age of 51 years. It was noted that almost one third of the participants were obese.

Phase 3 – BNT162b2-Naïve Subjects Assigned to Receive BNT162b2$_{SA}$ who Received Booster Dose of BNT162b2 (30 µg)

Table 33: Demographic Characteristics – Phase 3 – BNT162b2-Naïve Subjects Assigned to Receive BNT162b2SA Who Received Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)
	BNT162b2 (30 µg) (N[a]=242) n[b] (%)
Sex	
Male	123 (50.8)
Female	119 (49.2)
Race	
White	184 (76.0)
Black or African American	34 (14.0)
Asian	19 (7.9)
Multiracial	4 (1.7)
Not reported	1 (0.4)
Racial designation	
Japanese	1 (0.4)
Ethnicity	
Hispanic/Latino	30 (12.4)
Non-Hispanic/non-Latino	211 (87.2)
Not reported	1 (0.4)
Country	
USA	242 (100.0)
Age at booster vaccination (years)	
Mean (SD)	37.3 (10.60)
Median	38.0
Min, max	(18, 56)
Body mass index (BMI)	
Underweight (<18.5 kg/m^2)	2 (0.8)
Normal weight (≥18.5-24.9 kg/m^2)	83 (34.3)
Overweight (≥25.0-29.9 kg/m^2)	85 (35.1)
Obese (≥30.0 kg/m^2)	72 (29.8)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 05MAY2023 (11:39)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adsl_s005_na_d3

Assessor´s comment

Among the 242 subjects, the distribution between gender was 51% male and 49% female. The age of the included subjects ranged from 18-56 years with a median age of 38 years. The study was executed in USA and almost one third were obese.

Phase 3 BNT162b2-Experienced Subjects who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose)

Table 34: Demographic Characteristics – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose) – Booster Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (5 µg)		BNT162b2 (10 µg)	
	18-55 Years (N[a]=26) n[b] (%)	>55 Years (N[a]=53) n[b] (%)	18-55 Years (N[a]=25) n[b] (%)	>55 Years (N[a]=51) n[b] (%)
Sex				
Male	13 (50.0)	30 (56.6)	16 (64.0)	21 (41.2)
Female	13 (50.0)	23 (43.4)	9 (36.0)	30 (58.8)
Race				
White	16 (61.5)	40 (75.5)	17 (68.0)	39 (76.5)
Black or African American	3 (11.5)	3 (5.7)	3 (12.0)	2 (3.9)
Asian	4 (15.4)	10 (18.9)	4 (16.0)	7 (13.7)
Native Hawaiian or other Pacific Islander	1 (3.8)	0	1 (4.0)	0
Multiracial	2 (7.7)	0	0	2 (3.9)
Not reported	0	0	0	1 (2.0)
Racial designation				
Japanese	0	1 (1.9)	0	3 (5.9)
Ethnicity				
Hispanic/Latino	6 (23.1)	4 (7.5)	3 (12.0)	4 (7.8)
Non-Hispanic/non-Latino	20 (76.9)	49 (92.5)	22 (88.0)	47 (92.2)
Country				
USA	26 (100.0)	53 (100.0)	25 (100.0)	51 (100.0)
Age at booster vaccination (years)				
Mean (SD)	40.2 (8.63)	64.5 (6.16)	40.8 (10.98)	64.0 (5.80)
Median	40.0	63.0	44.0	63.0
Min, max	(25, 55)	(56, 83)	(19, 55)	(56, 79)
Body mass index (BMI)				
Underweight (<18.5 kg/m^2)	0	0	0	1 (2.0)
Normal weight (≥18.5-24.9 kg/m^2)	8 (30.8)	12 (22.6)	9 (36.0)	19 (37.3)
Overweight (≥25.0-29.9 kg/m^2)	10 (38.5)	26 (49.1)	6 (24.0)	19 (37.3)
Obese (≥30.0 kg/m^2)	8 (30.8)	15 (28.3)	10 (40.0)	12 (23.5)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 28JUN2023 (00:21)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_G4_6MPD_CSR/adsl_s005_g4_6m_saf

Assessor´s comment

Among the subjects that received BNT162b2, the age ranged between 19-83 years, the distribution between gender was in general similar except for the two different dose groups and it was noted that about one third of the subjects were obese. The study was executed in the USA.

Phase 3 – BNT162b2-Experienced Subjects who Were Previously Rerandomised/Assigned to Receive Booster Dose(s), and Received an Additional Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 19

Table 35: Demographic Characteristics – Phase 3 – BNT162b2-Experienced Subjects Who Were Previously Rerandomised/Assigned to Receive Booster Dose(s), and Received an Additional Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 19 – Booster Safety Population

	Previous Booster Vaccine Group (as Administered)				
	Vaccine Group (as Administered)				
	BNT162b2 (30 µg) (N[a]=182) n[b] (%)	BNT162b2$_{SA}$ (30 µg) (N[a]=199) n[b] (%)	BNT162b2 (5 µg) (N[a]=33) n[b] (%)	BNT162b2 (10 µg) (N[a]=38) n[b] (%)	BNT162b2$_{SA}$ (30 µg, 2 Doses) (N[a]=15) n[b] (%)
Sex					
Male	79 (43.4)	96 (48.2)	21 (63.6)	17 (44.7)	11 (73.3)
Female	103 (56.6)	103 (51.8)	12 (36.4)	21 (55.3)	4 (26.7)
Race					
White	148 (81.3)	161 (80.9)	24 (72.7)	31 (81.6)	13 (86.7)
Black or African American	19 (10.4)	22 (11.1)	3 (9.1)	1 (2.6)	2 (13.3)
American Indian or Alaska Native	2 (1.1)	1 (0.5)	0	0	0
Asian	7 (3.8)	13 (6.5)	5 (15.2)	6 (15.8)	0
Native Hawaiian or other Pacific Islander	0	0	1 (3.0)	0	0
Multiracial	4 (2.2)	0	0	0	0
Not reported	2 (1.1)	2 (1.0)	0	0	0
Racial designation					
Japanese	0	0	0	1 (2.6)	0
Ethnicity					
Hispanic/Latino	56 (30.8)	52 (26.1)	2 (6.1)	5 (13.2)	2 (13.3)
Non-Hispanic/non-Latino	126 (69.2)	142 (71.4)	31 (93.9)	33 (86.8)	12 (80.0)
Not reported	0	5 (2.5)	0	0	1 (6.7)
Country					
USA	182 (100.0)	199 (100.0)	33 (100.0)	38 (100.0)	15 (100.0)
Age at the additional booster dose of BNT162b2 (30 µg) (years)					
Mean (SD)	42.0 (9.28)	41.3 (9.83)	56.1 (14.25)	56.5 (15.46)	46.1 (9.52)
Median	43.0	42.0	61.0	60.5	47.0
Min, max	(22, 56)	(20, 63)	(26, 82)	(20, 80)	(23, 57)
Body mass index (BMI)					
Underweight (<18.5 kg/m^2)	1 (0.5)	3 (1.5)	0	0	0
Normal weight (≥18.5-24.9 kg/m^2)	47 (25.8)	44 (22.1)	11 (33.3)	16 (42.1)	2 (13.3)
Overweight (≥25.0-29.9 kg/m^2)	62 (34.1)	75 (37.7)	14 (42.4)	14 (36.8)	8 (53.3)
Obese (≥30.0 kg/m^2)	72 (39.6)	77 (38.7)	8 (24.2)	8 (21.1)	5 (33.3)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adsl Table Generation: 05MAY2023 (11:39)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adsl_s005_p3_d4

Assessor´s comment

The age ranged from 20-80 years. Obesity was noted in 21-40% of the subjects in each group. The distribution between gender was in general similar, however, in the smallest groups (n=33 BNT162b2 5µg and BNT162b2$_{SA}$ 30 µg) a slightly higher frequency of male was noted. The study was executed in the USA.

7.1.3. Phase 2/3, subjects aged 12-15 years

Disposition and Exposure

Table 36: Disposition of Subjects – Phase 2/3 Subjects 12 Through 15 Years of Age at the Time of Receiving the First Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Assigned)
	BNT162b2 (30 µg) (N[a]=825) n[b] (%)
Received booster vaccination	825 (100.0)
Completed booster vaccination period[c]	819 (99.3)
Discontinued from booster vaccination period but continued in the study	0
Discontinued from booster vaccination period	6 (0.7)
Reason for discontinuation from booster vaccination period	
Lost to follow-up	6 (0.7)
Withdrawn from the study	176 (21.3)
Reason for withdrawal	
Lost to follow-up	25 (3.0)
Protocol deviation	20 (2.4)
Withdrawal by subject	6 (0.7)
Withdrawal by parent/guardian	1 (0.1)
Other	124 (15.0)

a. N = number of assigned subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Booster vaccination period: from booster vaccination to the 1-month follow-up visit after the booster vaccination.
PFIZER CONFIDENTIAL SDTM Creation: 18NOV2022 (20:06) Source Data: adds Table Generation: 29NOV2022 (22:00)
(Data Cutoff Date: 03NOV2022, Database Snapshot Date: 16NOV2022) Output File: ./nda2_unblinded/C4591001_Peds_6MPD3/adds_s002_d3_ped_rand

The BNT162b2 booster safety population included 825 participants 12 through 15 years of age who previously received the BNT162b2 (30 µg) 2-dose series in Phase 2/3 of the study and were assigned to receive a booster (Dose 3) of BNT162b2 (30 µg). All safety analyses in this report present data after the booster dose from the 825 participants in the BNT162b2 (30 µg) booster group. All participants received the booster vaccination, of BNT162b2 (30 µg), as assigned.

Table 37: Vaccine Administration Timing – Phase 2/3 Subjects 12 Through 15 Years of Age at the Time of Receiving the First Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Assigned)
	BNT162b2 (30 µg) (N[a]=825) n[b] (%)
Assigned	825 (100.0)
Booster vaccination[c]	825 (100.0)
<8 Months	233 (28.2)
≥8-<10 Months	169 (20.5)
≥10-<12 Months	16 (1.9)
≥12-<14 Months	312 (37.8)
≥14-<16 Months	78 (9.5)
≥16 Months	17 (2.1)
Mean (SD)	10.8 (2.94)
Median	11.2
Min, max	(6.3, 20.1)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Months calculated since second dose of BNT162b2.
PFIZER CONFIDENTIAL SDTM Creation: 18NOV2022 (20:06) Source Data: adsl Table Generation: 05DEC2022 (00:38)
(Data Cutoff Date: 03NOV2022, Database Snapshot Date: 16NOV2022) Output File: ./nda2_unblinded/C4591001_Peds_6MPD3/advx_s002_time_d3_ped

Follow-up Time

Most participants (86.9%) had follow-up time ≥6 months after Dose 3 of BNT162b2 (30 µg), with a median follow-up time of 9.5 months (range: 1.5 to 10.7 m,onths) (Table 6). The median follow-up time since completion of the 2-dose series was 18.1 months (range: 11.5 to 25.8 months).

Table 38: Follow-up Time After Booster Dose – Phase 2/3 Subjects 12 Through 15 Years of Age at the Time of Receiving the First Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Administered)
	BNT162b2 (30 µg) (N[a]=825) n[b] (%)
Total exposure from booster vaccination to the cutoff date	
<6 Months	108 (13.1)
≥6-<7 Months	34 (4.1)
≥7-<8 Months	48 (5.8)
≥8-<9 Months	103 (12.5)
≥9-<10 Months	390 (47.3)
≥10-<11 Months	142 (17.2)
Mean (SD)	8.7 (1.70)
Median	9.5
Min, max	(1.5, 10.7)
Total exposure from second dose of BNT162b2 to the cutoff date	
<18 Months	382 (46.3)
≥18-<19 Months	84 (10.2)
≥19-<20 Months	11 (1.3)
≥20-<21 Months	14 (1.7)
≥21-<22 Months	16 (1.9)
≥22-<23 Months	150 (18.2)
≥23-<24 Months	142 (17.2)
≥24 Months	26 (3.2)
Mean (SD)	19.5 (3.19)
Median	18.1
Min, max	(11.5, 25.8)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 18NOV2022 (20:06) Source Data: adsl Table Generation: 23NOV2022 (22:11)
(Data Cutoff Date: 03NOV2022, Database Snapshot Date: 16NOV2022) Output File: ./nda2_unblinded/C4591001_Peds_6MPD3/adsl_fup_d3_ped

Demographics

Most participants in the Phase 3 BNT162b2 booster safety population were White (83.5%), with 4.6% Black or African American participants. There were 10.8% Hispanic/Latino participants. The median age at the time of Dose 3 administration was 14.0 years ranging from 13 through 15 years, and 49.3% of participants were male. Obese participants made up 12.1% of the booster safety population.

Table 39: Demographic Characteristics – Phase 2/3 Subjects 12 Through 15 Years of Age at the Time of Receiving the First Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)
	BNT162b2 (30 µg) (N[a]=825) n[b] (%)
Sex	
Male	407 (49.3)
Female	418 (50.7)
Race	
White	689 (83.5)
Black or African American	38 (4.6)
American Indian or Alaska Native	3 (0.4)
Asian	62 (7.5)
Native Hawaiian or other Pacific Islander	1 (0.1)
Multiracial	26 (3.2)
Not reported	6 (0.7)
Ethnicity	
Hispanic/Latino	89 (10.8)
Non-Hispanic/non-Latino	734 (89.0)
Not reported	2 (0.2)
Country	
USA	825 (100.0)
Age at booster vaccination (years)	
Mean (SD)	14.1 (0.80)
Median	14.0
Min, max	(13, 15)
Obese[c]	
Yes	100 (12.1)
No	725 (87.9)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Obese is defined as BMI ≥95th percentile from the growth chart. The obese status is based on data collected at Visit 1. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
PFIZER CONFIDENTIAL SDTM Creation: 18NOV2022 (20:06) Source Data: adsl Table Generation: 28NOV2022 (08:26)
(Data Cutoff Date: 03NOV2022, Database Snapshot Date: 16NOV2022) Output File: ./nda2_unblinded/C4591001_Peds_6MPD3/adsl_s005_d3_ped_saf

Assessor´s comment

In the Phase 2/3 study that included 825 subjects aged 12-15 years of age, the median age was 14 years. All subjects received the booster dose, six of them discontinued the study due to lost to follow-up. Withdrawal from study was reported among 176 subjects (21%), most common reason was "other" (n=124). The study was executed in the USA and the distribution between gender were similar. The median follow-up time after first booster dose was 9.5 months and from Dose 2 18.1 months. The median time from Dose 2 to booster dose was 11.2 months (range 6.3-20.1 months).

7.2. Results

7.2.1. Phase 1

Dose 1 to 6 Months after Dose 2

Reactogenicity was reported previously for these participants and therefore not included here.

Two SAEs were reported by 1 participant in the BNT162b2 20-µg group and 1 participant in the 30-µg group. In the BNT162b2 20-µg group, 1 SAE of appendicitis was reported in 1 participant and was assessed by the investigator as not related to study intervention. In the BNT162b2 30-µg group, 1 severe SAE of neuritis was reported by 1 participant and was assessed by the investigator as not related to
study intervention.

First Booster Dose to 1 Month after the First Booster Dose

Overview of AEs are illustrated in the table below.

Table 40: Number (%) of Subjects Reporting at Least 1 Adverse Event From the First Booster Dose to 1 Month After the First Booster Dose – Phase 1 – Subjects Who Received the First Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Initial Vaccine Group (as Administered)							
	BNT162b1				BNT162b2			
Adverse Event	10 µg (N[a]=21) n[b] (%)	20 µg (N[a]=24) n[b] (%)	30 µg (N[a]=24) n[b] (%)	100 µg (N[a]=9) n[b] (%)	10 µg (N[a]=22) n[b] (%)	20 µg (N[a]=23) n[b] (%)	30 µg (N[a]=24) n[b] (%)	Placebo (N[a]=28) n[b] (%)
Any adverse event	2 (9.5)	5 (20.8)	4 (16.7)	1 (11.1)	3 (13.6)	1 (4.3)	1 (4.2)	0
Related[c]	1 (4.8)	1 (4.2)	3 (12.5)	0	3 (13.6)	0	0	0
Severe	0	0	2 (8.3)	0	0	0	0	0
Life-threatening	0	0	0	1 (11.1)	0	0	0	0
Any serious adverse event	0	0	0	1 (11.1)	0	0	0	0
Related[c]	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Life-threatening	0	0	0	1 (11.1)	0	0	0	0
Any nonserious adverse event	2 (9.5)	5 (20.8)	4 (16.7)	0	3 (13.6)	1 (4.3)	1 (4.2)	0
Related[c]	1 (4.8)	1 (4.2)	3 (12.5)	0	3 (13.6)	0	0	0
Severe	0	0	2 (8.3)	0	0	0	0	0
Life-threatening	0	0	0	0	0	0	0	0
Any adverse event leading to withdrawal	0	0	0	0	0	0	0	0
Related[c]	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any adverse event," n = number of subjects reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adae Table Generation: 05MAY2023 (03:03)
(Database Snapshot Date: 28APR2023) Output File: ./nda2 unblinded/C4591001 CSR/adae s091 p1 d3

A limited number of AEs by SOC were reported by Phase 1 participants from the first booster dose to 1 month after the first booster dose. Generally, most Preferred Terms (PTs) were reported by no more than 1 participant per the initial BNT162b1 and BNT162b2 dose groups and included, but not limited to, reports of lymphadenopathy, fatigue, axillary pain, chills, myalgia, muscle spasms, dizziness, headache, paresthesia, and presyncope. One participant (4.2%) reported an AE of deep vein thrombosis toxicity grade 2, 29 days after the booster dose. The subject was in the initial BNT162b1 20-µg group, and the event was not considered related to vaccination.

Related AEs

Related AEs were reported in the initial BNT162b1 10-, 20-, and 30-µg groups and the initial BNT162b2 10-µg group only. Related AEs were reported by no more than 3 participants per group.

From the first booster dose to 1 month after the first booster dose, AEs assessed as related by the investigator in the initial BNT162b1 10- and 20-µg groups were reported by no more than 1 participant per group. Two participants (8.3%) in the initial 30-µg dose group reported a related AE of lymphadenopathy.

In the initial BNT162b2 10-µg group, general disorders and administration site conditions (chills, injection site haemorrhage) and nervous system disorders (paraesthesia and headache) were reported by 2 participants (9.1%) each.

Immediate AEs

There were no immediate adverse events reported after the first booster dose in the initial BNT162b1 groups. In the initial BNT162b2 10-µg group, 1 immediate AE of injection site haemorrhage was reported in 1 participant.

Severe or life-threatening AEs

From the first booster dose to 1 month after the first booster dose, 2 severe events (axillary pain and headache) were reported by 2 participants (8.3%) in the initial BNT162b1 30-µg group. One life-threatening (Grade 4) event of colitis was reported in the initial BNT162b1 100-µg group, onset 4 days after booster vaccination, and was assessed by the investigator as unrelated to study vaccine.

SAEs and death

No deaths were reported in the Phase 1 booster safety population in the initial BNT162b1 and BNT162b2 groups from the first booster dose to 1 month after the first booster dose.

From booster dose (Dose 3) to 1 month after booster dose of BNT162b2 30 µg, 1 participant (11.1%) in the initial BNT162b1 100-µg group reported 1 SAE of colitis which was assessed by the investigator as unrelated to the vaccine. This participant required overnight observation at the emergency room due to symptoms of abdominal pain, diarrhoea, and blood in stool, with the diagnosis confirmed by CT scan of the abdomen. Treatment was with oral antibiotics and a follow up sigmoidoscopy was negative with full resolution of symptoms 19 days after onset.

Discontinuation from study due to AEs

No participants in the Phase 1 BNT162b2 booster safety population in the initial BNT162b1 and BNT162b2 groups were withdrawn due to AEs from the first booster dose of BNT162b2 (30 µg) to 1 month after the first booster dose.

Pregnancy

One pregnancy was reported in the Phase 1 BNT162b2 booster safety population in the initial BNT162b1 group from the first booster dose of BNT162b2 (30 µg) to 1 month after the first booster dose.

<u>Additional Booster Dose to 1 Month After the Additional Booster Dose</u>

From Dose 4 to 1 month after Dose 4, the number (%) of participants with any AE was 3 (3.8%); these AEs were considered by investigators as related to study intervention. No participants reported a severe or life-threatening AE. No event of pregnancy was reported. No SAEs, AEs leading to withdrawal, or deaths were reported.

The study did not use e-diary to collect reactogenicity events after the additional booster dose (Dose 4). Events related to reactogenicity (i.e., injection site pain, myalgia, pyrexia, and headache) were collected as AEs. Of the AEs reported during this period, some were reactogenicity events reported as AEs. The number of participants (%) who reported AEs by SOC for these reactogenicity terms are as follows:

- general disorders and administration site conditions: 1 (1.3%)
- musculoskeletal and connective tissue disorders: 2 (2.5%)

From the additional booster dose to 1 month after the additional booster dose, 3 participants (3.8%) had AEs assessed by the investigator as related to study intervention. These events, which also included reactogenicity events, were reported as AEs. One participant (1.3%) each reported injection site pain, myalgia, and pain in extremity.

MAH Conclusion

All doses of BNT162b1 and BNT162b2 were safe and well tolerated. BNT162b1 at 100µg was discontinued due to the reactogenicity profile (previously reported); no participants in either age group received any dose of BNT162b2 at the 100-µg dose level.

The frequency of participants with any AE after the booster doses (Dose 3 and Dose 4) of BNT162b2 (30 µg) was low, with most participants reporting mild, reactogenicity-type events.

The frequency of participants reporting SAEs after the first 2 doses of BNT162b1 and BNT162b2, and the booster doses (Dose 3 and Dose 4), was from none to low, and all SAEs reported were assessed by the investigator as not related to study intervention. There were no AEs leading to withdrawal or deaths reported.

Assessor´s comment:

Local and systemic events for these participants was presented in the initial application for EMEA/H/C/005735/0000.

From the first booster to one month after the first booster dose of BNT162b2 30 µg, most of the reported AEs were related to reactogenicity. One event of deep vein thrombosis (DVT) not considered related to the vaccination was reported in one participant. Two events of related lymphadenopathy were reported. One event of immediate haemorrhage was reported in one participant.

The reported AEs after the administered booster doses in the Phase 1 study are in line with what has previously been observed for the primary series.

7.2.2. Phase 2/3

Local Reactions and Systemic Events

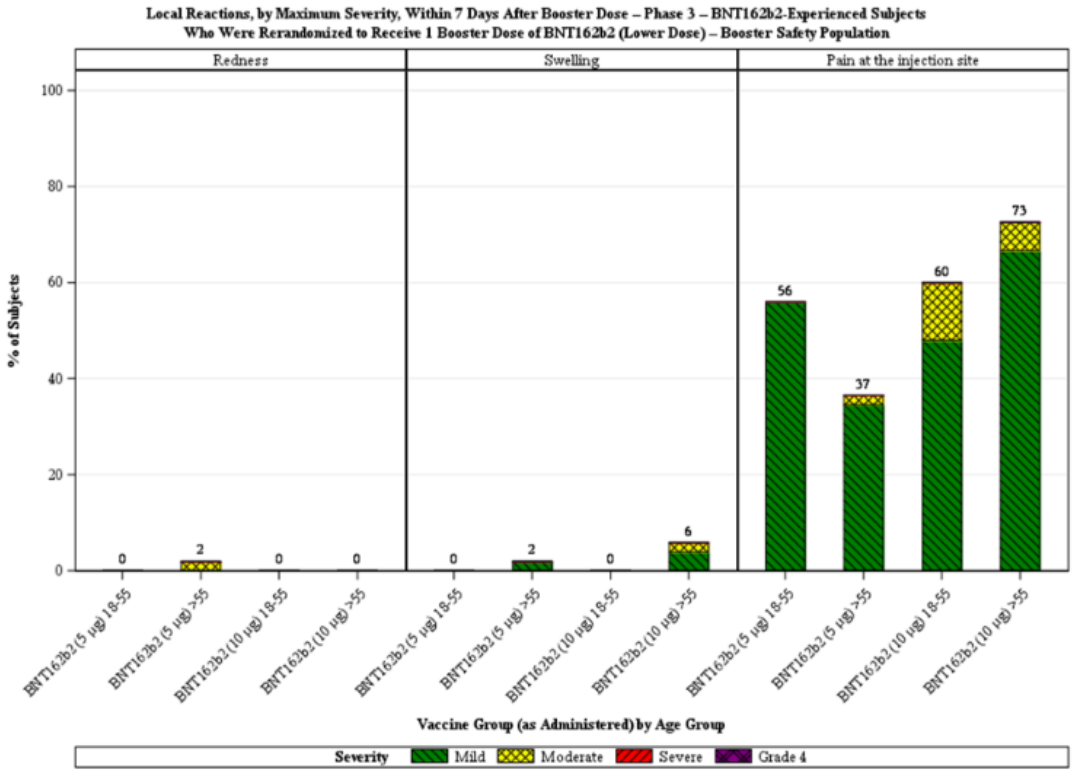
Reactogenicity for subjects receiving primary series of BNT162b2 30µg has been reported previously.

Local reactions and systemic events for BNT162b2-experienced participants 18 through 55 and >55 years of age who were rerandomised to receive 1 booster dose of BNT162b2 (lower dose of 5 or 10 µg) under protocol amendment 15 are presented in this final CSR.

Local Reactions and Systemic Events for Participants who Received Lower Dose Booster

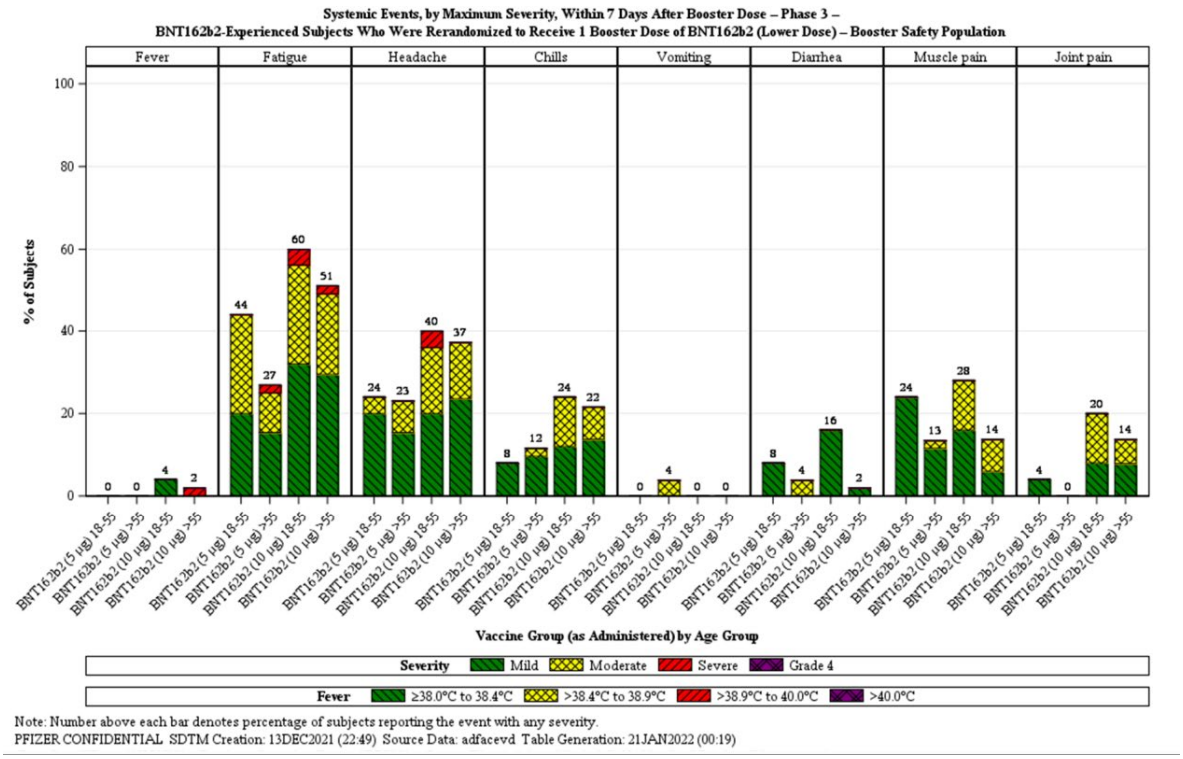
Local reactions and systemic events in BNT162b2-experienced participants 18 through 55 and >55 years of age who received 1 booster dose of BNT162b2 (5 or 10 µg) were mild to moderate at intensity, as illustrated below.

Figure 3: Subjects Reporting Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose Phase 3 BNT162b2-Experienced Subjects Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose) Booster Safety Population



Note: Number above each bar denotes percentage of subjects reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 13DEC2021 (22:49) Source Data: adfacevd Table Generation: 21JAN2022 (00:19)
(Data Cutoff Date: 22NOV2021, Database Snapshot Date: 10DEC2021) Output File: /nda2_unblinded/C4591001_G4_LD/adce_f001_lr_g4_6m

Figure 4: Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose Phase 3 BNT162b2-Experienced Subjects Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose) Booster Safety Population



Assessor´s comment

Among the subjects that had received a low dose booster dose (BNT162b2 at 5 or 10 µg), showed a similar reactogenicity profile as what has been observed from the primary series. No subjects who received BNT162b2 5 µg reported fever. There was a clear trend to lower reactogenicity with lower dose and lower reactogenicity in subjects aged >55 years compared to subjects aged 18-54 years.

Adverse Events from Dose 1 to 6 months after Dose 2

Final SAE analyses are reported for participants ≥16 years of age from Dose 1 to 6 months after Dose 2 during the blinded, placebo-controlled and open label follow-periods.

SAEs dose 1 up to 6 months after dose 2

From Dose 1 to 6 months after Dose 2 of BNT162b2, 291 participants (1.3%) in the placebo group reported SAEs after receiving placebo. All SAEs were assessed by the investigator as not related to study intervention.

From Dose 1 to 6 months after Dose 2 of BNT162b2, participants who reported at least 1 SAE were similar in the original BNT162b2 group (428 participants [2.0%]) and original placebo/BNT162b2 group (353 participants [1.7%]).

In the original BNT162b2 (30 µg) group, there were 3 participants with an SAE each assessed by the investigator as related to study intervention:

- One participant experienced a ventricular arrhythmia that occurred 1 day after Dose 2 of BNT162b2 and resolved within 8 days.
- One participant experienced a shoulder injury related to vaccine administration that resolved 153 days after Dose 2 of BNT162b2 administration.

- One participant experienced paresthesia that occurred 47 days after Dose 2 of BNT162b2, which lasted 221 days and resolved.

In the original placebo/BNT162b2 (30 µg) group, 3 participants had an SAE assessed by the investigator as related to study intervention:

- One participant experienced an SAE of portal vein thrombosis that occurred 61 days after Dose 2 of BNT162b2, which lasted 8 days and resolved.
- One participant experienced a transient ischemic attack that occurred 5 days after Dose 2 of BNT162b2, which lasted 1 day and resolved.
- One participant experienced myalgia that occurred 59 days after Dose 2 of BNT162b2, which lasted for 51 days and resolved.

There were no clinically meaningful differences in SAEs by age group, race, sex, or ethnicity.

Assessor´s comment

From the first dose up to 6 months after the second dose, a similar frequency of SAEs was reported in the vaccine group and in the placebo group (2% vs 1.7%).

No new safety concerns were detected here.

First Booster Dose to 1 Month After the First Booster Dose of BNT162b2 (30 µg)

Brief Summary of AEs, Phase 2/3 Participants who Received Booster Dose of BNT162b2 (30 µg)

Table 41: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose – Phase 2/3 – Subjects Who Received Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 18 – Booster Safety Population

Adverse Event	Vaccine Group (as Administered) BNT162b2 (30 µg) 12-15 Years (N[a]=825) n[b] (%)	Vaccine Group (as Administered) BNT162b2 (30 µg) ≥16 Years (N[a]=22470) n[b] (%)
Any adverse event	153 (18.5)	3818 (17.0)
Related[c]	139 (16.8)	3377 (15.0)
Severe	6 (0.7)	90 (0.4)
Life-threatening	1 (0.1)	6 (0.0)
Any serious adverse event	2 (0.2)	65 (0.3)
Related[c]	0	3 (0.0)
Severe	2 (0.2)	40 (0.2)
Life-threatening	1 (0.1)	6 (0.0)
Any nonserious adverse event	153 (18.5)	3779 (16.8)
Related[c]	139 (16.8)	3377 (15.0)
Severe	6 (0.7)	52 (0.2)
Life-threatening	0	0
Any adverse event leading to withdrawal	0	1 (0.0)
Related[c]	0	0
Severe	0	0
Life-threatening	0	1 (0.0)
Death	0	1 (0.0)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any adverse event," n = number of subjects reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adae Table Generation: 05MAY2023 (03:01)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adae_s091_p23_d3

Participants With Confirmed Stable HIV Disease Who Received Booster Dose of BNT162b2 (30 µg)

From Dose 3 to 1 month after Dose 3, the number of participants with any AE was 11 (11.2%). Events considered by the investigator as related to study intervention were reported by 8 participants (8.2%). No participants reported a severe AE. No AEs leading to withdrawals or deaths were reported.

BNT162b2-Naïve Participants Assigned to Receive BNT162b2$_{SA}$ Who Received Booster Dose of BNT162b2 (30 µg)

From Dose 3 to 1 month after Dose 3, the number of participants with any AE was 27 (11.4%). Events considered by the investigator as related to study intervention were reported by 25 participants (10.6%). No participants reported a severe AE. No AEs leading to withdrawals or deaths were reported.

Analysis of Adverse Events

Participants 12 Through 15 Years of Age and ≥16 Years of Age who Received Booster Dose of BNT162b2 (30 µg)

The most commonly reported AE in both age groups was injection site pain, in 66 participants (8.0%) in the 12 through 15 years of age group and 1679 (7.5%) in the ≥16 years of age group. Most AEs reported during this period reflect reactogenicity events reported as AEs. AE frequencies by reactogenicity SOC for both groups (12 through 15 years of age and ≥16 years of age) were:

- general disorders and administration site conditions (130 [15.8%] and 2923 [13.0%])
- nervous system disorders (49 [5.9%] and 632 [2.8%])
- musculoskeletal and connective tissue disorders (19 [2.3%] and 646 [2.9%])
- gastrointestinal disorders (12 [1.5%] and 203 [0.9%])

- Lymphadenopathy was reported by 8 and 360 participants (1.0% and 1.6%) in the 12 through 15 years of age and ≥16 years of age groups, respectively.

There were no clinically important differences regarding the percentage of participants reporting at least 1 AE by SOC and PT in the subgroup analyses by age, race, sex, and ethnicity from the administration of Dose 3 of BNT162b2 (30 µg) to 1 month after Dose 3.

Participants With Confirmed Stable HIV Disease who Received Booster Dose of BNT162b2 (30 µg)

From Dose 3 to 1 month after Dose 3, AEs were most commonly reported in the SOC of general disorders and administration site conditions (7 participants [7.1%]), followed by gastrointestinal disorders (2 participants [2.0%]).

BNT162b2-Naïve Participants Assigned to Receive BNT162b2$_{SA}$ who Received Booster Dose of BNT162b2 (30 µg)

From Dose 3 to 1 month after Dose 3, AEs were most commonly reported in the SOC of general disorders and administration site conditions (23 participants [9.7%]) followed by musculoskeletal and connective tissue disorders (6 participants [2.5%]).

Assessor´s comment

From the first booster dose up to one month after the first booster dose of BNT162b2 30 µg, the frequency of any AEs was 17% (n=3818) among the subjects ≥16 years of age, many of them were considered related to study vaccine (15% [n=3377]) and most of them were reactogenicity events. There was no difference among the subjects that had a confirmed stable HIV disease who received a booster dose. Among the BNT162b2-naïve subjects that received a booster dose, the reported AES was mostly related to reactogenicity.

No new safety concern was detected here.

Related Adverse Events

Related AEs Phase 2/3 Participants who Received Booster Dose of BNT162b2 (30 µg)

From Dose 3 to 1 month after Dose 3, 3377 participants (15.0%) in the ≥16 years of age group had AEs assessed by the investigator as related to study intervention. The most common related event was injection site pain, reported in 1678 participants (7.5%) in the ≥16 years of age group. Most of the other related AEs were reactogenicity events in the SOC of general disorders and administration site conditions, reported by 2910 (13.0%) in the ≥16 years of age group. Headache was reported by 550 participants (2.4%) in the ≥16 years of age group.

BNT162b2-Naïve Participants Assigned to Receive BNT162b2$_{SA}$ who Received Booster Dose of BNT162b2 (30 µg)

From Dose 3 to 1 month after Dose 3, 25 BNT162b2-naïve participants (10.6%) assigned to receive BNT162b2SA who received the booster dose of BNT162b2 (30 µg) had AEs assessed by the investigators as related to study intervention. The most common related event was injection site pain in 11 participants (4.7%).

Assessor´s comment

Among the subjects that received a booster dose, pain at injection site was the most commonly reported related AE. Most of the related AEs concerned reactogenicity. The same pattern was observed among the BNT162b2-naïve subjects.

No new safety concern was detected here.

Immediate Adverse Events

Phase 2/3 Participants who Received Booster Dose of BNT162b2 (30 µg)

The frequencies of immediate AEs reported within 30 minutes after the booster dose were low (≤ 0.4%) in the 12 through 15 years of age and ≥16 years of age groups. 26 participants reported injection site pain and 6 participants reported fatigue in the ≥16 years of age group. In addition, in the ≥16 years of age group, 31 participants (0.1%) reported immediate AEs in the SOC of injury, poisoning and procedural complications with 20 participants (0.1%) reporting exposure during pregnancy.

There were no immediate AEs reported in the BNT162b2-naïve booster safety population (assigned to Receive BNT162b2$_{SA}$) after receiving the booster dose.

Assessor´s comment

Few immediate AEs was reported after the booster dose of BNT162b2 30 µg.

No new safety concern was detected here.

Severe or Life-Threatening Adverse Events

Phase 2/3 Participants who Received Booster Dose of BNT162b2 (30 µg)

From Dose 3 to 1 month after Dose 3, severe events in participants ≥16 years of age were reported in 90 participants (0.4%). Life-threatening (or Grade 4) events were reported in 6 participants ≥16 years of age from booster dose to 1 month after booster dose. Of the 6 reported life-threatening events, 1 was considered by the investigator as related to study intervention: Angioedema reported in 1 participant, occurred 1 day after Dose 3 with a duration of 2 days. The event was reported as an SAE and resolved, and the participant continued in the study.

There were no severe or life-threatening AEs reported in BNT162b2-naïve participants assigned to Receive BNT162b2$_{SA}$ who received the booster dose of BNT162b2 (30 µg).

Assessor´s comment

One severe event of angioedema which was considered related to the booster dose was reported. The event occurred one day after the booster dose and resolved after two days. Angioedema is already listed as an adverse reaction in the SmPC at the frequency uncommon.

Deaths

One death was reported in the booster dose BNT162b2 (30 µg) ≥16 years of age group. The participant died 22 days after Dose 3 with the cause of death provided as adenocarcinoma of the pancreas which was considered unrelated to study intervention.

Serious Adverse Events (SAEs)

Phase 2/3 Participants who Received Booster Dose of BNT162b2 (30 µg)

Table 42: Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 2/3 – Subjects Who Received Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 18 – Booster Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (30 µg) 12-15 Years (N[a]=825) n[b] (%)	(95% CI[c])	≥16 Years (N[a]=22470) n[b] (%)	(95% CI[c])
Any adverse event	2 (0.2)	(0.0, 0.9)	65 (0.3)	(0.2, 0.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Splenic vein thrombosis	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
CARDIAC DISORDERS	0	(0.0, 0.4)	9 (0.0)	(0.0, 0.1)
Acute coronary syndrome	0	(0.0, 0.4)	2 (0.0)	(0.0, 0.0)
Angina pectoris	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Atrial fibrillation	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Atrioventricular block	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Cardiac failure	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Coronary artery disease	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Myocarditis	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Supraventricular tachycardia	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
EAR AND LABYRINTH DISORDERS	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Deafness neurosensory	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
GASTROINTESTINAL DISORDERS	0	(0.0, 0.4)	7 (0.0)	(0.0, 0.1)
Abdominal pain upper	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Colitis	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Dysphagia	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Gastrointestinal haemorrhage	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Rectal haemorrhage	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Small intestinal obstruction	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Volvulus	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	(0.0, 0.4)	2 (0.0)	(0.0, 0.0)
Chest discomfort	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Chest pain	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
HEPATOBILIARY DISORDERS	0	(0.0, 0.4)	8 (0.0)	(0.0, 0.1)
Cholecystitis acute	0	(0.0, 0.4)	2 (0.0)	(0.0, 0.0)
Alcoholic liver disease	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Biliary obstruction	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Cholecystitis	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Hepatic cirrhosis	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Hepatitis acute	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Hyperbilirubinaemia neonatal	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Jaundice cholestatic	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
INFECTIONS AND INFESTATIONS	0	(0.0, 0.4)	11 (0.0)	(0.0, 0.1)
Appendicitis	0	(0.0, 0.4)	3 (0.0)	(0.0, 0.0)
Appendicitis perforated	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Cellulitis	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Complicated appendicitis	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Diverticulitis	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Focal peritonitis	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Gastroenteritis norovirus	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Osteomyelitis	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Pneumonia	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Pyelonephritis acute	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Wound infection	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	(0.0, 0.4)	6 (0.0)	(0.0, 0.1)
Cervical vertebral fracture	0	(0.0, 0.4)	2 (0.0)	(0.0, 0.0)
Road traffic accident	0	(0.0, 0.4)	2 (0.0)	(0.0, 0.0)
Ankle fracture	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Exposure during pregnancy	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Overdose	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
METABOLISM AND NUTRITION DISORDERS	0	(0.0, 0.4)	2 (0.0)	(0.0, 0.0)
Hypoglycaemia neonatal	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Hyponatraemia	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	(0.0, 0.4)	2 (0.0)	(0.0, 0.0)
Back pain	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Kyphosis	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (30 µg) 12-15 Years (N[a]=825) n[b] (%)	(95% CI[c])	≥16 Years (N[a]=22470) n[b] (%)	(95% CI[c])
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	(0.0, 0.4)	10 (0.0)	(0.0, 0.1)
Adenocarcinoma of colon	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Adenocarcinoma pancreas	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Colon cancer	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Endometrial adenocarcinoma	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Gastrointestinal stromal tumour	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Intraductal proliferative breast lesion	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Invasive breast carcinoma	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Papillary thyroid cancer	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Prostate cancer	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Renal neoplasm	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
NERVOUS SYSTEM DISORDERS	0	(0.0, 0.4)	7 (0.0)	(0.0, 0.1)
Cerebrovascular accident	0	(0.0, 0.4)	2 (0.0)	(0.0, 0.0)
Haemorrhage intracranial	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Hepatic encephalopathy	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Intracranial aneurysm	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Neuropathy peripheral	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Seizure	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	(0.0, 0.4)	2 (0.0)	(0.0, 0.0)
Abortion spontaneous	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Gestational hypertension	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
PSYCHIATRIC DISORDERS	2 (0.2)	(0.0, 0.9)	2 (0.0)	(0.0, 0.0)
Alcohol abuse	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Anxiety	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Depression	1 (0.1)	(0.0, 0.7)	0	(0.0, 0.0)
Suicidal ideation	1 (0.1)	(0.0, 0.7)	0	(0.0, 0.0)
Suicide attempt	1 (0.1)	(0.0, 0.7)	0	(0.0, 0.0)
RENAL AND URINARY DISORDERS	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Renal colic	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Angioedema	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
VASCULAR DISORDERS	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Aneurysm	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)
Aortic aneurysm	0	(0.0, 0.4)	1 (0.0)	(0.0, 0.0)

Note: MedDRA (v25.1) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of subjects 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: 10MAR2023 (16:40) Source Data: adae Table Generation: 05MAY2023 (03:09)
(Database Snapshot Date: 28APR2023) Output File: ./nda2 unblinded/C4591001 CSR/adae s130 sae p23 d3

In the ≥16 years age groups, 2 participants had SAEs assessed by the investigator as related to study intervention:

- One 30 to 40-year-old participant experienced an SAE of spontaneous abortion toxicity grade 1 that occurred 13 days after Dose 3.
- An SAE of myocarditis of Grade 3 severity was reported in one 16-18-year-old male participant, 4 days following the booster dose. The SAE lasted for 101 days, and the event resolved with sequalae.

There were no clinically important differences regarding the percentage of participants reporting at least 1 SAE in the subgroup analyses by age, race, sex, and ethnicity from the administration of Dose 3 of BNT162b2 (30 µg) to 1 month after Dose 3.

Among the BNT162b2-naïve participants assigned to receive $BNT162b2_{SA}$ who received booster dose of BNT162b2 (30 µg), there were no SAEs reported after receiving the booster dose.

Assessor´s comment

The frequency of SAE was <0,5% among the subjects ≥12 years of age that received a booster dose of BNT162b2 30 µg. One SAE of myocarditis was reported. Myocarditis is already listed in the SmPC both in section 4.4 and 4.8. One event of spontaneous abortion toxicity grade 1 was reported 13 days after vaccination, the participant had an additional miscarriage 105 days after vaccination which was not considered related to the vaccination. The investigator considered the first spontaneous abortion to be possible related with the vaccination, which was not agreed by the MAH. The opinion of the MAH can be supported since the presented data does not allow to conclude upon a possible relation to vaccination.

Discontinuation from Study due to AEs

One participant in the ≥16 years of age group had an AE leading to withdrawal that was considered by the investigator as not related to study intervention (adenocarcinoma of the pancreas).

No participants in the population of BNT162b2-naïve participants assigned to receive BNT162b2$_{SA}$ who received booster dose of BNT162b2 (30 µg) were withdrawn due to AEs from Dose 3 to 1 month after Dose 3.

Assessor´s comment

One participant discontinued the study due to adenocarcinoma of the pancreas which was not considered related to vaccination.

Pregnancy

One pregnancy was reported in BNT162b2-Naïve participants assigned to received BNT162b2$_{SA}$ who received booster dose of BNT162b2 (30 µg).

First Booster to 1 and 6 Months after Booster Dose (Lower Doses)

BNT162b2 (5 µg) Groups

From the BNT162b2 (5 µg) booster dose to 1 month after the booster dose, the number of BNT162b2-experienced participants with any AE was 3 and 2 participants (11.5% and 3.8%) in the 18 through 55 years of age and >55 years of age groups, respectively. One participant (1.9%) reported a related AE in the >55 years of age group. No participants reported severe AEs, SAEs, AEs leading to withdrawal, or deaths in either age group. Through 6 months after the booster dose, AEs were reported by 2 additional participants >55 years of age, with 1 participant (1.9%) reporting an SAE that was assessed by the
investigator as not related to study intervention. No AEs leading to withdrawal or deaths were reported in either of the age groups.

BNT162b2 (10 µg) Groups

From the BNT162b2 (10 µg) booster dose to 1 month after the booster dose, 2 (8.0%) participants 18 through 55 years of age reported an AE. No participants in the >55 years of age group reported any AEs. One participant (4.0%) reported a related AE in the 18 through 55 years of age group. No SAEs, AEs leading to withdrawal, or deaths were reported in either of the age groups.

Through 6 months after the booster dose, AEs were reported 6 months after the booster dose by 1 additional participant each in 18 through 55 years of age and >55 years of age. No SAEs, AEs leading to withdrawal, or deaths were reported in either of the age groups.

AEs by SOC and preferred term from the administration of a booster dose of BNT162b2 (lower dose of 5 or 10 µg) to BNT162b2-experienced participants rerandomised to receive a booster dose of

BNT162b2 (lower dose of 5 or 10 µg), through 1 month and 6 months after the booster dose, are presented below.

Table 43: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose) – Booster Safety Population

	Vaccine Group (as Administered)							
	BNT162b2 (5 µg)				BNT162b2 (10 µg)			
	18-55 Years (N[a]=26)		>55 Years (N[a]=53)		18-55 Years (N[a]=25)		>55 Years (N[a]=51)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	3 (11.5)	(2.4, 30.2)	2 (3.8)	(0.5, 13.0)	2 (8.0)	(1.0, 26.0)	0	(0.0, 7.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	(0.0, 13.2)	0	(0.0, 6.7)	1 (4.0)	(0.1, 20.4)	0	(0.0, 7.0)
Lymphadenopathy	0	(0.0, 13.2)	0	(0.0, 6.7)	1 (4.0)	(0.1, 20.4)	0	(0.0, 7.0)
GASTROINTESTINAL DISORDERS	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	1 (4.0)	(0.1, 20.4)	0	(0.0, 7.0)
Gastrooesophageal reflux disease	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	1 (4.0)	(0.1, 20.4)	0	(0.0, 7.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
Fatigue	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	0	(0.0, 13.7)	0	(0.0, 7.0)
Skin laceration	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	0	(0.0, 13.7)	0	(0.0, 7.0)
METABOLISM AND NUTRITION DISORDERS	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
Dehydration	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	0	(0.0, 13.7)	0	(0.0, 7.0)
Pain in extremity	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	0	(0.0, 13.7)	0	(0.0, 7.0)
NERVOUS SYSTEM DISORDERS	0	(0.0, 13.2)	2 (3.8)	(0.5, 13.0)	0	(0.0, 13.7)	0	(0.0, 7.0)
Dizziness	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
Dysgeusia	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)

Note: MedDRA (v25.1) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of subjects 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: 10MAR2023 (16:40) Source Data: adae Table Generation: 29JUN2023 (02:14)
(Database Snapshot Date: 28APR2023) Output File: ./nda2 unblinded/C4591001 G4 6MPD CSR/adae s130 g4 1m6

Table 44: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 6 Months After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomised to Receive 1 Booster Dose of BNT162b2 (Lower Dose) – Booster Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (5 µg) 18-55 Years (N[a]=26) n[b] (%)	(95% CI[c])	>55 Years (N[a]=53) n[b] (%)	(95% CI[c])	BNT162b2 (10 µg) 18-55 Years (N[a]=25) n[b] (%)	(95% CI[c])	>55 Years (N[a]=51) n[b] (%)	(95% CI[c])
Any adverse event	3 (11.5)	(2.4, 30.2)	4 (7.5)	(2.1, 18.2)	3 (12.0)	(2.5, 31.2)	1 (2.0)	(0.0, 10.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	(0.0, 13.2)	0	(0.0, 6.7)	1 (4.0)	(0.1, 20.4)	0	(0.0, 7.0)
Lymphadenopathy	0	(0.0, 13.2)	0	(0.0, 6.7)	1 (4.0)	(0.1, 20.4)	0	(0.0, 7.0)
EAR AND LABYRINTH DISORDERS	0	(0.0, 13.2)	0	(0.0, 6.7)	0	(0.0, 13.7)	1 (2.0)	(0.0, 10.4)
Deafness unilateral	0	(0.0, 13.2)	0	(0.0, 6.7)	0	(0.0, 13.7)	1 (2.0)	(0.0, 10.4)
Vertigo	0	(0.0, 13.2)	0	(0.0, 6.7)	0	(0.0, 13.7)	1 (2.0)	(0.0, 10.4)
GASTROINTESTINAL DISORDERS	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	2 (8.0)	(1.0, 26.0)	0	(0.0, 7.0)
Gastrooesophageal reflux disease	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	1 (4.0)	(0.1, 20.4)	0	(0.0, 7.0)
Haemorrhoids	0	(0.0, 13.2)	0	(0.0, 6.7)	1 (4.0)	(0.1, 20.4)	0	(0.0, 7.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
Fatigue	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	0	(0.0, 13.7)	0	(0.0, 7.0)
Skin laceration	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	0	(0.0, 13.7)	0	(0.0, 7.0)
METABOLISM AND NUTRITION DISORDERS	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
Dehydration	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (3.8)	(0.1, 19.6)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
Back pain	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
Pain in extremity	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	0	(0.0, 13.7)	0	(0.0, 7.0)
Temporomandibular joint syndrome	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	0	(0.0, 13.7)	0	(0.0, 7.0)
NERVOUS SYSTEM DISORDERS	0	(0.0, 13.2)	2 (3.8)	(0.5, 13.0)	0	(0.0, 13.7)	0	(0.0, 7.0)
Dizziness	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
Dysgeusia	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
RENAL AND URINARY DISORDERS	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
Nephrolithiasis	0	(0.0, 13.2)	1 (1.9)	(0.0, 10.1)	0	(0.0, 13.7)	0	(0.0, 7.0)
SURGICAL AND MEDICAL PROCEDURES	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	0	(0.0, 13.7)	0	(0.0, 7.0)
Endodontic procedure	1 (3.8)	(0.1, 19.6)	0	(0.0, 6.7)	0	(0.0, 13.7)	0	(0.0, 7.0)

Note: MedDRA (v25.1) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of subjects 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: 10MAR2023 (16:40) Source Data: adae Table Generation: 29JUN2023 (02:14)
(Database Snapshot Date: 28APR2023) Output File: ./nda2 unblinded/C4591001 G4 6MPD CSR/adae s130 g4 6m

Related Adverse Events

Related AEs were reported by 1 participant (1.9%) in the BNT162b2 (5 µg) >55 years of age group only and included general disorders and administration site conditions (fatigue), metabolism and

nutrition disorders (dehydration), and nervous system disorders (dizziness). One participant (4.0%) reported a related AE of lymphadenopathy in the BNT162b2 (10 µg) 18 through 55 years of age group.

Immediate Adverse Events

There were no immediate AEs reported in the BNT162b2-experienced (lower dose) booster safety population after the booster dose.

Severe or Life-Threatening Adverse Events

There were no severe or life-threatening AEs reported in BNT162b2-experienced (lower dose) booster safety population after the booster dose.

Deaths

No deaths were reported in the BNT162b2-experienced (lower dose) safety population from the booster dose to 6 months after the booster dose.

Serious Adverse Events

From booster dose (BNT162b2 5 or 10 µg) to 6 months after booster dose 1 participant (1.9%) in the BNT162b2 (5 µg) >55 years of age group reported 1 SAE of back pain, which was assessed by the investigator as unrelated to the vaccine.

Discontinuations from Study Due to Adverse Events

No participants in the Phase 3 BNT162b2 (lower dose) booster safety population were withdrawn due to AEs from booster dose to 6 months after booster dose.

Other Significant Adverse Events

One participant (2.0%) reported a significant AE of unilateral deafness in the BNT162b2 (10 µg) >55 years of age group that began approximately 2 and a half months after receipt of booster vaccination and was assessed by the investigator as not related to study intervention.

Assessor´s comment

No new safety concerns were detected among the subjects that received low booster dose (BNT162b2 at 5 or 10 µg). No SAEs, AEs leading to withdrawal, or deaths were reported. Most of the reported AEs were related to reactogenicity.

Additional Booster Dose to 1 Month After Additional Booster Dose of BNT162b2 30 µg

Brief Summary of Adverse Events

Table 45: Number (%) of Subjects Reporting at Least 1 Adverse Event From the Additional Booster Dose to 1 Month After the Additional Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Previously Rerandomised/Assigned to Receive Booster

Dose(s), and Received an Additional Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 19 – Booster Safety Population

	Previous Booster Vaccine Group (as Administered)				
Adverse Event	BNT162b2 (30 µg) (N[a]=182) n[b] (%)	BNT162b2$_{5A}$ (30 µg) (N[a]=196) n[b] (%)	BNT162b2 (5 µg) (N[a]=33) n[b] (%)	BNT162b2 (10 µg) (N[a]=38) n[b] (%)	BNT162b2$_{5A}$ (30 µg, 2 Doses) (N[a]=15) n[b] (%)
Any adverse event	17 (9.3)	17 (8.7)	0	1 (2.6)	1 (6.7)
Related[c]	14 (7.7)	16 (8.2)	0	1 (2.6)	0
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Any serious adverse event	0	1 (0.5)	0	0	0
Related[c]	0	0	0	0	0
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Any nonserious adverse event	17 (9.3)	17 (8.7)	0	1 (2.6)	1 (6.7)
Related[c]	14 (7.7)	16 (8.2)	0	1 (2.6)	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 subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any adverse event," n = number of subjects reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adae Table Generation: 05MAY2023 (03:03)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adae_s091_p3_d4

Analysis of AEs by SOCs and PTs

Table 46: Number (%) of Subjects Reporting at Least 1 Adverse Event From the Additional Booster Dose to 1 Month After the Additional Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Previously

Rerandomised/Assigned to Receive Booster Dose(s), and Received an Additional Booster Dose of BNT162b2 (30 µg) as Part of Protocol Amendment 19 – Booster Safety Population

System Organ Class Preferred Term	Previous Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=182) n[b] (%)	(95% CI[c])	BNT162b2$_{SA}$ (30 µg) (N[a]=196) n[b] (%)	(95% CI[c])	BNT162b2 (5 µg) (N[a]=33) n[b] (%)	(95% CI[c])	BNT162b2 (10 µg) (N[a]=38) n[b] (%)	(95% CI[c])	BNT162b2$_{SA}$ (30 µg, 2 Doses) (N[a]=15) n[b] (%)	(95% CI[c])
Any adverse event	17 (9.3)	(5.5, 14.5)	17 (8.7)	(5.1, 13.5)	0	(0.0, 10.6)	1 (2.6)	(0.1, 13.8)	1 (6.7)	(0.2, 31.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (1.1)	(0.1, 3.9)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Lymphadenopathy	2 (1.1)	(0.1, 3.9)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
CARDIAC DISORDERS	0	(0.0, 2.0)	1 (0.5)	(0.0, 2.8)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Atrial fibrillation	0	(0.0, 2.0)	1 (0.5)	(0.0, 2.8)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	13 (7.1)	(3.9, 11.9)	14 (7.1)	(4.0, 11.7)	0	(0.0, 10.6)	1 (2.6)	(0.1, 13.8)	0	(0.0, 21.8)
Injection site pain	9 (4.9)	(2.3, 9.2)	8 (4.1)	(1.8, 7.9)	0	(0.0, 10.6)	1 (2.6)	(0.1, 13.8)	0	(0.0, 21.8)
Fatigue	4 (2.2)	(0.6, 5.5)	5 (2.6)	(0.8, 5.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Chills	2 (1.1)	(0.1, 3.9)	2 (1.0)	(0.1, 3.6)	0	(0.0, 10.6)	1 (2.6)	(0.1, 13.8)	0	(0.0, 21.8)
Pyrexia	3 (1.6)	(0.3, 4.7)	1 (0.5)	(0.0, 2.8)	0	(0.0, 10.6)	1 (2.6)	(0.1, 13.8)	0	(0.0, 21.8)
Pain	1 (0.5)	(0.0, 3.0)	3 (1.5)	(0.3, 4.4)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Axillary pain	0	(0.0, 2.0)	1 (0.5)	(0.0, 2.8)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Injection site swelling	1 (0.5)	(0.0, 3.0)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
INFECTIONS AND INFESTATIONS	1 (0.5)	(0.0, 3.0)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Ear infection	1 (0.5)	(0.0, 3.0)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.5)	(0.0, 3.0)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Corneal abrasion	1 (0.5)	(0.0, 3.0)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
INVESTIGATIONS	1 (0.5)	(0.0, 3.0)	1 (0.5)	(0.0, 2.8)	0	(0.0, 10.6)	0	(0.0, 9.3)	1 (6.7)	(0.2, 31.9)
Blood cholesterol increased	1 (0.5)	(0.0, 3.0)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Blood testosterone decreased	0	(0.0, 2.0)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	1 (6.7)	(0.2, 31.9)
Body temperature increased	0	(0.0, 2.0)	1 (0.5)	(0.0, 2.8)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (2.7)	(0.9, 6.3)	4 (2.0)	(0.6, 5.1)	0	(0.0, 10.6)	1 (2.6)	(0.1, 13.8)	0	(0.0, 21.8)
Myalgia	3 (1.6)	(0.3, 4.7)	3 (1.5)	(0.3, 4.4)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Arthralgia	1 (0.5)	(0.0, 3.0)	1 (0.5)	(0.0, 2.8)	0	(0.0, 10.6)	1 (2.6)	(0.1, 13.8)	0	(0.0, 21.8)
Back pain	1 (0.5)	(0.0, 3.0)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Intervertebral disc protrusion	0	(0.0, 2.0)	1 (0.5)	(0.0, 2.8)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Muscular weakness	0	(0.0, 2.0)	1 (0.5)	(0.0, 2.8)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
NERVOUS SYSTEM DISORDERS	1 (0.5)	(0.0, 3.0)	4 (2.0)	(0.6, 5.1)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Headache	1 (0.5)	(0.0, 3.0)	4 (2.0)	(0.6, 5.1)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.5)	(0.0, 3.0)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)
Erythema	1 (0.5)	(0.0, 3.0)	0	(0.0, 1.9)	0	(0.0, 10.6)	0	(0.0, 9.3)	0	(0.0, 21.8)

Note: MedDRA (v25.1) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of subjects 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: 10MAR2023 (16:40) Source Data: adae Table Generation: 05MAY2023 (03:03)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adae_s130_p3_d4

Related Adverse Events by System Organ Class and Preferred Term

Related AEs were reported in the BNT162b2 (30 µg), BNT162b2$_{SA}$ (30 µg), and BNT162b2$_{SA}$ (10 µg) groups.

In the BNT162b2 (30 µg) and BNT162b2$_{SA}$ (30 µg) groups, most related AEs reported were reactogenicity-type events and generally included injection site pain, pyrexia, headache, fatigue, myalgia, and chills.

There were no related AEs reported in the BNT162b2 (5 µg) and BNT162b2SA (30 µg, 2 doses) groups. There was 1 participant reported related AE in the BNT162b2 (10 µg) group.

Immediate Adverse Events

There were no participants in any of the groups who reported any immediate AEs after the additional booster dose of BNT162b2 (30 µg).

Severe or Life-Threatening Adverse Events

There were no participants in any of the groups who reported any severe or life-threatening AEs after the additional booster dose of BNT162b2 (30 µg).

Deaths

There were no deaths reported in participants after the additional booster dose of BNT162b2 (30 µg).

Serious Adverse Events

From the additional booster dose to 1 month after the booster dose, 1 participant (0.5%) reported an SAE in the BNT162b2SA (30 µg) group that was assessed by the investigator as not related to study intervention.

Discontinuations From Study Due to Adverse Events

No participants in the BNT162b2 were withdrawn due to AEs after the additional booster dose of BNT162b2 (30 µg).

Assessor´s comment

Among the subjects (N=467) that received a second booster dose (protocol amendment 14, 15 and 19) of either BNT162b2 at 5, 10, 30 µg or BNT162b2$_{SA}$ 30 µg, a higher frequency of any AEs was noted among the subjects that received 30 µg (7-9%) compared with those who received low dose i.e., 5 or 10 µg (0-3%). The most commonly reported events were typical for reactogenicity.

No new safety concern was detected here.

MAH Conclusion

Data previously presented from this clinical study showed that the primary 2 dose series of BNT162b2 30 µg was highly effective against symptomatic COVID-19, including cases that were severe and/or resulted in hospitalisation, prior to the emergence of the Omicron variant.

Additional efficacy data presented in this CSR show that BNT162b2 30 µg likely also provides some protection against asymptomatic SARS-CoV-2 infection in an analysis conducted prior to the emergence of Omicron. In addition, the cumulative incidence of confirmed COVID-19 cases increased as multiple SARS-CoV-2 variants circulated, most notably following the emergence of Omicron. This resulted in the development and implementation of variant-adapted vaccines: bivalent vaccines targeting the original/wild type strain and Omicron BA.1 or BA.4/BA.5, and most recently monovalent XBB.1.5.
Overall immunogenicity responses were similar for lower booster doses (Dose 3) of BNT162b2 (5 or 10 µg) in the BNT162b2 5- and 10-µg groups, and SARS-CoV-2 neutralizing GMTs substantially increased at 1 month after the lower booster dose. In addition, administration of lower booster dose of BNT162b2 (5 or 10 µg) was safe and tolerable.

The primary 2-dose series for BNT162b1 and BNT162b2 at doses of 10, 20, and 30 µg was safe and tolerable. Administration of booster dose(s) (Dose 3, 4, or 5) of BNT162b2 30 µg to participants who had completed the 2-dose series showed continued safety and tolerability with most AEs consistent with reactogenicity-type events, and no new safety concerns.

7.2.3. Phase 2/3, subjects aged 12-15 years.

Local Reactions and Systemic Events

There are no analyses of local reactions and/or systemic events in this report because solicited reactogenicity was not collected using e-diaries after the booster dose (Dose 3), but rather as unsolicited AEs on the case report form.

Adverse Events

An overview of AEs from administration of Dose 3 one month after Dose 3 is shown below.

Table 47: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose – Phase 2/3 Subjects 12 Through 15 Years of Age at the Time of Receiving the First Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)
Adverse Event	BNT162b2 (30 µg) (N[a]=825) n[b] (%)
Any adverse event	152 (18.4)
Related[c]	139 (16.8)
Severe	6 (0.7)
Life-threatening	1 (0.1)
Any serious adverse event	2 (0.2)
Related[c]	0
Severe	2 (0.2)
Life-threatening	1 (0.1)
Any nonserious adverse event	152 (18.4)
Related[c]	139 (16.8)
Severe	6 (0.7)
Life-threatening	0
Any adverse event leading to withdrawal	0
Related[c]	0
Severe	0
Life-threatening	0
Death	0

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any adverse event," n = number of subjects reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational vaccine.
PFIZER CONFIDENTIAL SDTM Creation: 18NOV2022 (20:04) Source Data: adae Table Generation: 23NOV2022 (20:12)
(Data Cutoff Date: 03NOV2022, Database Snapshot Date: 16NOV2022) Output File: ./nda2_unblinded/C4591001_Peds_6MPD3/adae_s091_1mpd3_ped_saf

From Dose 3 to the data cut-off date (03 November 2022), in addition to the 152 participants who reported AEs up to 1 month after Dose 3, 9 additional participants reported an AE, for a cumulative number of participants with any AE of 161 (19.5%). As of the cut-off date, events considered by the investigator as related to study intervention remained the same as at 1 month after Dose 3, reported by 139 participants (16.8%). In addition to the 6 participants with a severe AE that were reported up to 1 month after Dose 3, as of the data cut-off date there were 3 additional participants who reported a severe AE; which were also considered unrelated by the investigator.

The most commonly reported AE was injection site pain, in 66 participants (8.0%). Most AEs reported during this period reflect reactogenicity events reported by the investigator as AEs. AE frequencies in SOCs for such reactogenicity terms were:

- general disorders and administration site conditions: 15.8%
- nervous system disorders: 5.9%
- musculoskeletal and connective tissue disorders: 2.3%

- gastrointestinal disorders: 1.5%.
- Lymphadenopathy was reported by 8 (1.0%) participants.

AEs reported from Dose 3 to 1 month after Dose 3 by SOC and preferred term are presented below.

Table 48: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 2/3 Subjects 12 Through 15 Years of Age at the Time of Receiving the First Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=825)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Any adverse event	152 (18.4)	(15.8, 21.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	8 (1.0)	(0.4, 1.9)
Lymphadenopathy	8 (1.0)	(0.4, 1.9)
CARDIAC DISORDERS	1 (0.1)	(0.0, 0.7)
Ventricular extrasystoles	1 (0.1)	(0.0, 0.7)
GASTROINTESTINAL DISORDERS	12 (1.5)	(0.8, 2.5)
Nausea	9 (1.1)	(0.5, 2.1)
Vomiting	5 (0.6)	(0.2, 1.4)
Abdominal pain	1 (0.1)	(0.0, 0.7)
Abdominal pain upper	1 (0.1)	(0.0, 0.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	130 (15.8)	(13.3, 18.4)
Injection site pain	66 (8.0)	(6.2, 10.1)
Fatigue	61 (7.4)	(5.7, 9.4)
Pyrexia	28 (3.4)	(2.3, 4.9)
Pain	24 (2.9)	(1.9, 4.3)
Chills	22 (2.7)	(1.7, 4.0)
Injection site erythema	5 (0.6)	(0.2, 1.4)
Malaise	3 (0.4)	(0.1, 1.1)
Axillary pain	1 (0.1)	(0.0, 0.7)
INFECTIONS AND INFESTATIONS	1 (0.1)	(0.0, 0.7)
Abscess jaw	1 (0.1)	(0.0, 0.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (0.5)	(0.1, 1.2)
Cartilage injury	1 (0.1)	(0.0, 0.7)
Contusion	1 (0.1)	(0.0, 0.7)
Fall	1 (0.1)	(0.0, 0.7)
Forearm fracture	1 (0.1)	(0.0, 0.7)
Ligament sprain	1 (0.1)	(0.0, 0.7)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	19 (2.3)	(1.4, 3.6)
Myalgia	13 (1.6)	(0.8, 2.7)
Pain in extremity	6 (0.7)	(0.3, 1.6)
Musculoskeletal chest pain	1 (0.1)	(0.0, 0.7)
NERVOUS SYSTEM DISORDERS	49 (5.9)	(4.4, 7.8)
Headache	47 (5.7)	(4.2, 7.5)
Dizziness	2 (0.2)	(0.0, 0.9)
Syncope	1 (0.1)	(0.0, 0.7)
PSYCHIATRIC DISORDERS	8 (1.0)	(0.4, 1.9)
Depression	3 (0.4)	(0.1, 1.1)
Anxiety	2 (0.2)	(0.0, 0.9)
Nightmare	2 (0.2)	(0.0, 0.9)
Aggression	1 (0.1)	(0.0, 0.7)
Insomnia	1 (0.1)	(0.0, 0.7)
Major depression	1 (0.1)	(0.0, 0.7)
Suicidal ideation	1 (0.1)	(0.0, 0.7)
Suicide attempt	1 (0.1)	(0.0, 0.7)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (0.2)	(0.0, 0.9)
Dysmenorrhoea	1 (0.1)	(0.0, 0.7)
Intermenstrual bleeding	1 (0.1)	(0.0, 0.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	(0.0, 0.7)
Nasal congestion	1 (0.1)	(0.0, 0.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.2)	(0.0, 0.9)
Dermatitis contact	1 (0.1)	(0.0, 0.7)
Sensitive skin	1 (0.1)	(0.0, 0.7)
SURGICAL AND MEDICAL PROCEDURES	1 (0.1)	(0.0, 0.7)
Oral surgery	1 (0.1)	(0.0, 0.7)

Note: MedDRA (v25.1) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of subjects 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: 18NOV2022 (20:04) Source Data: adae Table Generation: 23NOV2022 (20:12)
(Data Cutoff Date: 03NOV2022, Database Snapshot Date: 16NOV2022) Output File:
./nda2 unblinded/C4591001 Peds 6MPD3/adae s130 1md3 ped saf

Related AEs

From Dose 3 to 1 month after Dose 3, 139 participants (16.8%) had AEs assessed by the investigator as related to study intervention (table below). The most common related event was injection site pain, in 65 participants (7.9%). Most of the other related AEs were reactogenicity events in the SOC of general disorders and administration site conditions, reported by 129 participants (15.6%) and headache reported by 47 participants (5.7%).

Table 49: Number (%) of Subjects Reporting at Least 1 Related Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 2/3 Subjects 12 Through 15 Years of Age at the Time of Receiving the First Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=825)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Any adverse event	139 (16.8)	(14.4, 19.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	7 (0.8)	(0.3, 1.7)
Lymphadenopathy	7 (0.8)	(0.3, 1.7)
GASTROINTESTINAL DISORDERS	12 (1.5)	(0.8, 2.5)
Nausea	9 (1.1)	(0.5, 2.1)
Vomiting	5 (0.6)	(0.2, 1.4)
Abdominal pain	1 (0.1)	(0.0, 0.7)
Abdominal pain upper	1 (0.1)	(0.0, 0.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	129 (15.6)	(13.2, 18.3)
Injection site pain	65 (7.9)	(6.1, 9.9)
Fatigue	61 (7.4)	(5.7, 9.4)
Pyrexia	28 (3.4)	(2.3, 4.9)
Pain	24 (2.9)	(1.9, 4.3)
Chills	22 (2.7)	(1.7, 4.0)
Injection site erythema	4 (0.5)	(0.1, 1.2)
Malaise	3 (0.4)	(0.1, 1.1)
Axillary pain	1 (0.1)	(0.0, 0.7)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	18 (2.2)	(1.3, 3.4)
Myalgia	13 (1.6)	(0.8, 2.7)
Pain in extremity	6 (0.7)	(0.3, 1.6)
NERVOUS SYSTEM DISORDERS	49 (5.9)	(4.4, 7.8)
Headache	47 (5.7)	(4.2, 7.5)
Dizziness	2 (0.2)	(0.0, 0.9)
Syncope	1 (0.1)	(0.0, 0.7)
PSYCHIATRIC DISORDERS	2 (0.2)	(0.0, 0.9)
Insomnia	1 (0.1)	(0.0, 0.7)
Nightmare	1 (0.1)	(0.0, 0.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	(0.0, 0.7)
Nasal congestion	1 (0.1)	(0.0, 0.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.1)	(0.0, 0.7)
Sensitive skin	1 (0.1)	(0.0, 0.7)

Note: MedDRA (v25.1) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of subjects 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: 18NOV2022 (20:04) Source Data: adae Table Generation: 23NOV2022 (20:12)
(Data Cutoff Date: 03NOV2022, Database Snapshot Date: 16NOV2022) Output File:
./nda2 unblinded/C4591001 Peds 6MPD3/adae s130 rel 1mpd3 ped saf

Immediate Adverse Events

The frequencies of immediate AEs reported within 30 minutes after the booster dose were ≤0.4%, with 2 participants reporting injection site pain and 1 participant reporting fatigue.

Assessor´s comment

Among the 825 subjects aged 12-15 years who received a booster dose of BNT162b2 30 µg, 18% reported any AEs. Most of these AEs were reactogenicity events (general disorders and administration site conditions and headache) and were considered related to vaccination. Pyrexia was reported in 28 (3.4%) of the subjects. Two events of lymphadenopathy were reported, lymphadenopathy is already listed as an adverse reaction in the SmPC.

Two events of immediate AEs were reported: fatigue and injection site pain.

The results are in line with previous results and no new safety concern was detected here.

Severe or Life-Threatening Adverse Events

From Dose 3 to 1 month after Dose 3, 8 severe events (pyrexia [N=3 (0.4%)], depression [N=2] (0.2%), and one (0.1%) each of aggression, suicidal ideation, and dysmenorrhea) were reported by 6 (0.7%) participants. One life-threatening (Grade 4) event of a suicide attempt was assessed by the investigator as unrelated to the study vaccine.

Adverse Events from Dose 3 to the Data Cut-off Date

From Dose 3 to the data cut-off date (03 November 2022), which represents a median of 9.5 months of follow-up after Dose 3, the number of participants with any AE was 161 (19.5%). There were 9 additional participants that reported any AE beyond the 1-month after Dose 3 visit. The additional events were unrelated and included 3 Grade 3 SAEs (pectus excavatum, epiphyseal fracture and suicide ideation) and 2 Grade 4 SAEs (depressed fractured skull and subdural hematoma in the same participant).

Deaths

No deaths were reported in the Phase 3 BNT162b2 booster safety population as of the data cut-off date (03 November 2022).

Serious Adverse Events from Dose 3 to 1 Month After Dose 3

From Dose 3 to 1 month after Dose 3, 3 SAEs were reported by 2 participants (one participant reported depression, one participant reported suicidal ideation and suicide attempt) and were assessed by the investigator as unrelated to the vaccine.

Serious Adverse Events from Dose 3 to the Data Cut-off Date

From Dose 3 to the data cutoff date (03 November 2022), 8 SAEs were reported by 6 participants, including 3 SAEs reported by 2 participants after the 1-month follow-up visit after Dose 3. These 5 SAEs were assessed by the investigator as unrelated to the study vaccine and are summarized below.

- A SAE of pectus excavatum of Grade 3 severity, 97 days following the booster dose. The participant underwent repair surgery with nuss bar placement and the SAE was considered recovered/resolved 67 days after the date of onset.
- A SAE of epiphyseal fracture/growth plate fracture of right elbow of Grade 3 severity, 71 days following the booster dose that recovered/resolved 64 days after the date of onset.

- A SAE of suicide ideation of Grade 3 severity, 129 days following the booster dose that recovered/resolved 33 days after the date of onset.
- A participant reported 2 SAEs of traumatic left temporoparietal depressed skull fracture and traumatic subdural haematoma of Grade 4 severity, 110 days following the booster dose, resulting from an accident to the head that were recovering/resolving at the data cutoff date (03 November 2022).

Safety-Related Participant Withdrawals

No participants in the Phase 3 BNT162b2 booster safety population were withdrawn due to AEs from Dose 3 to the data cut-off date (03 November 2022).

Pregnancy

No pregnancies were reported in the Phase 2/3 BNT162b2 booster group from Dose 3 to the data cut-off date (03 November 2022).

Assessor´s comment

Three events of severe pyrexia were reported. From Dose 3 and up to the cut-off date (=3 Nov 2022), SAEs were reported by 6 participants (depression/worsening of depression and suicidal ideation/suicidal attempt, pectus excavatum, elbow fracture and skull fracture), none of the events were considered related to vaccination. No subjects were withdrawn due to AEs.

No new safety concern was detected here.

MAH Conclusion

In this report, safety data are evaluated from 825 participants 12 through 15 years of age with median follow-up of 9.5 months after Dose 3. The AE profile among adolescents reflects expected reactogenicity events, age-appropriate events consistent with the general population, with low incidence of severe events. The incidence of SAEs in adolescents was low. All SAEs, including all SAEs in the psychiatric disorders SOCs, were assessed by the investigator as not related to study intervention. No participants were withdrawn from the study because of an AE. No deaths occurred in the adolescent group. Review of AEs and SAEs suggested no new patterns or new safety signals among adolescents which continues to
support the safety of BNT162b2 administered as a booster dose to individuals 12 through 15 years of age.

7.3. Discussion

This report includes final data from the clinical study C4591001, listed as a category 3 study in the RMP. Safety interim data to support a proposed update in section 4.8 in the SmPC for adolescents aged 12-15 years who had received one booster dose of BNT162b2 30µg has also been provided.

Study C4591001 is a Phase 1/2/3 multicentre, multinational, randomised, placebo-controlled, observer-blind, dose finding, vaccine candidate-selection, and efficacy study in healthy individuals ≥12 years of age. The study was executed in the USA and consisted of 2 parts: Phase 1 to identify preferred vaccine candidate(s) and dose level(s) in individuals 18 through 55 and 65 through 85 years of age; and Phase 2/3 as an expanded cohort and efficacy part in individuals ≥12 years of age.

Phase 1

In the Phase 1 study, primary series of BNT162b1 (10, 20, 30, 100µg) and BNT162b2 (10, 20, 30 µg) was administered to subgroups including 24 adult subjects in each group (total n=195). Most of these subjects then received one booster dose of BNT162b2 (30 µg), and an additional booster dose was administered to about half of the study population. Median follow-up time since first booster dose was 12-21 months in the different initial vaccine groups, and the median follow-up time after the additional booster dose was 5-6 months. From the first booster to one month after the first booster dose, most of the reported AEs were related to reactogenicity. The reported AEs after the administered booster doses in the Phase 1 study are in line with what has previously been observed for the primary series.

Phase 2/3

The final disposition for all randomised subjects to the Phase 2/3 study C4591001 included a total of 46,406 subjects aged ≥12 years, of which 99.8% received the two doses included in the primary series of BNT162b2 30µg. Among the subjects who were originally randomised to placebo, 89-92% received two doses of BNT162b2 30µg. In total were 1,156 subjects withdrawn from the study, most of them due to lost to follow-up (n=543) or withdrawn by subject (n=397). The age ranged from 13-92 years, with a median age of 51 years. A total number of 23,406 participants in the Phase 2/3 study received a first booster dose, and 89% of them had completed the 6-month post-booster vaccination visit. Among the 22,581 subjects ≥16 years of age that received a booster vaccination, most of these vaccinations occurred 6-15 months after Dose 2. The median follow-up time after booster dose was 12.3 months.

From the first booster dose up to one month after the first booster dose of BNT162b2 30 µg, the frequency of any AEs was 17% (n=3,818) among the subjects ≥16 years of age, many of them were considered related to study vaccine (15% [n=3,377]) and most of them were reactogenicity events.

One severe event of angioedema which was considered related to the booster dose was reported. The event occurred one day after the booster dose and resolved after two days. Angioedema is already listed as an adverse reaction in the SmPC at the frequency uncommon.

One subject reported one SAE of myocarditis 4 days after he received the booster dose. The event resolved within 101 days. Myocarditis is already listed in the SmPC section 4.4 and 4.8.

Booster dose BA.1

BNT162b2-naïve adult subjects (n=330) received a dose of the variant vaccine BNT162b2SA (South Africa B.1.351). Among the BNT162b2-naïve subjects that received a dose of BNT162b2SA, the reported AES was mostly related to reactogenicity.

Low dose booster dose BNT162b2 at 5 or 10 µg

According to protocol amendment 14 and 15, adult subjects that had already received the primary series of BNT162b2 30 µg were rerandomised to receive one low dose booster of BNT162b2 at 5 µg (n=79) or 10 µg (76). None of the subjects that received BNT162b2 5 µg reported fever. There was a tendency to lower reactogenicity with lower dose and lower reactogenicity in subjects aged >55 years compared to subjects aged 18-54 years.

Additional booster dose, protocol amendment 19

Among the subjects (N=467) that received a second booster dose of either BNT162b2 at 5 µg (n=33), 10 µg (n=38), 30 µg (n=182) or BNT162b2SA 30 µg (n=211), a higher frequency of any AEs was noted among the subjects that received 30 µg (7-9%) compared with those who received low dose i.e., 5 or 10 µg (0-3%). The most reported events were typical for reactogenicity.

Subjects 12-15 years of age

In the Phase 2/3 study that included 825 subjects aged 12-15 years, the median age was 14 years. All subjects received the booster dose, six of them discontinued the study due to lost to follow-up. Withdrawal from study was reported among 176 subjects (21%), most common reason was "other" (n=124). The study was executed in the USA and the distribution between gender were similar. The median follow-up time after first booster dose was 9.5 months and from Dose 2 18.1 months. The median time from Dose 2 to booster dose was 11.2 months (range 6.3-20.1 months).

After the booster dose up to one month after the vaccination, 18% of the subjects reported any AEs. Most of these AEs were reactogenicity events (general disorders and administration site conditions and headache) and were considered related to vaccination. Two events of lymphadenopathy were reported, lymphadenopathy is already listed as an adverse reaction in the SmPC. Two events of immediate AEs were reported: fatigue and injection site pain. Three events of severe pyrexia were reported. From Dose 3 and up to the cut-off date (=3 Nov 2022), SAEs were reported by 6 participants (depression/worsening of depression and suicidal ideation/suicidal attempt, pectus excavatum, elbow fracture and skull fracture), none of the events were considered related to vaccination. No subjects were withdrawn due to AEs.

The results presented for participants aged 12-15 years supports the proposed update of the SmPC section 4.8.

8. Risk management plan

The MAH submitted an updated RMP version 10.1 (DLP 18 June 2023, dated 03 August 2023) with this type II variation application.

Table 50: Summary of significant changes in the RMP

RMP Part/Module	~~RMP 9.1~~ ~~Major Changes~~	~~RMP 9.2~~ ~~Major Changes~~	RMP 10.~~0~~1 ~~(9.3 + 9.4 +9.5)~~ Major Changes
PRODUCT(S) OVERVIEW	~~Addition of Comirnaty Original/Omicron BA.4-5 in infants and children aged 6 months to 4 years, (1.5/1.5 mcg) according to the updated SmPC.~~ ~~Updated to include primary vaccination course/booster dose to individuals 12 years of age and older and to children 5 to 11 years of age according to the updated SmPC.~~	~~Addition of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) according to the updated SmPC for Dark Blue and Light Blue cap vials.~~	Aligned with the ~~updated~~ current SmPC ~~(that includes simplified posology as requested by EMA).~~ Editorial changes to include the new strain XBB.1.5 (as per procedure EMEA/H/C/005735/II/0183).
Epidemiology of the Indication(s) and Target Populations	~~Updated to include the indication of Comirnaty original /Omicron BA.4-5 in i infants and children aged 6 months to 4 years.~~ ~~New references included~~	~~No changes made.~~	~~No changes made.~~ Editorial changes to include the new strain XBB.1.5.
Non-Clinical Part of the Safety Specification	~~No changes made.~~	~~No changes made.~~	No changes made.

RMP Part/Module	~~RMP 9.1~~ ~~Major Changes~~	~~RMP 9.2~~ ~~Major Changes~~	RMP 10.0~~0~~1 ~~(9.3 + 9.4 +9.5)~~ Major Changes
Clinical Trial Exposure	~~Addition of text and CT exposure tables from Studies C4591044 and C4591048, SSB and SSD (in scope for the submission) and Study C4591031 (SSC) for data completeness.~~ ~~Previous CT exposure of paediatric population (from the 2 to <5 years and 6 months to <2 years of age) from Study C4591007 has been moved to Annex 7.~~ ~~CT exposure data from Study C4591001 regarding booster (3rd) dose in 12–15 years of age has been added in Annex 7.~~	~~No changes made.~~	No changes made.
Populations Not Studied in Clinical Trials	~~Updates in SIV.3 (exposure of special population)~~	~~No changes made.~~	No changes made.
Post-Authorisation Experience	~~Updated with new DLP 18 December 2022~~	~~No changes made.~~	~~No changes made.~~ Updated as of 18 June 2023 (aligned with PSUR # 5)
Additional EU Requirements for the Safety Specification	~~No changes made.~~	~~No changes made.~~	No changes made.
Identified and Potential Risks	~~Reactogenicity data updated from studies C4591044 and C4591048 (SSB and SSD).~~ ~~The characterization of the important risks Myocarditis and Pericarditis and VAED/VAERD (CT and non-CT data) was updated for the 3 age groups: 12 years and older, 5 to <12 years of age and 6 months to <5 years of age (receiving bivalent Omicron BA.4-5) with new DLP as per table above.~~	~~No changes made.~~	~~Removal of the important identified risk VAED/VAERD.~~ ~~Editorial changes to remove the mention of study C4591010.~~ No changes made.
Summary of the Safety Concerns	~~No changes made.~~	~~No changes made.~~	~~Removal of the important identified risk VAED/VAERD.~~ No changes made.

RMP Part/Module	~~RMP 9.1~~ ~~Major Changes~~	~~RMP 9.2~~ ~~Major Changes~~	RMP 10.0~~0~~1 ~~(9.3 + 9.4 +9.5)~~ Major Changes
Routine Pharmacovigilance activities	~~Updated to add Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) formulation in the vial differentiation description.~~	~~Updated to add Comirnaty Original/Omicron BA.4-5 (5/5 mcg) for Dark Blue and Light Blue cap vials and Original/Omicron BA.4-5 (15/15 mcg) for Light Grey cap in the vial differentiation description and text revised.~~	Editorial changes to clean-up routine activities and remove PBS 30 mcg presentation from vial differentiation/ potential medication error. ~~remove the mention of VAED/VAERD DCA.~~ Updated to add Comirnaty Omicron XBB.1.5 presentations.
Additional Pharmacovigilance Activities and Summary Table of Additional Pharmacovigilance Activities	~~Updated to include editorial changes to confirm that it is feasible to assess safety concerns for Bivalent vaccine with studies C4591012 and C4591036, while it's not feasible to assess them with study C4591021.~~ ~~Editorial change of protocol amendment submission date of study C4591021.~~ ~~Addition of new NIS C4591051 and C4591052 and associated milestones.~~ ~~Other milestones updated.~~	~~Milestones updated for studies C4591031 (SSE) and C4591036.~~	~~According to PAM MEA 011.6 the study C4591010 is removed from the RMP.~~ Studies C4591001, BNT162-01 and WI235284 are removed. ~~Other milestones updated for studies C4591007, C4591015, C4591030.~~
PLANS FOR POST AUTHORISATION EFFICACY STUDIES	~~No changes made.~~	~~No changes made.~~	No changes made.
Routine Risk Minimisation Measures **Error! Reference source not found.**Additional Risk Minimisation Measures Summary of Risk Minimisation Measures	~~Updated based on the changes made in PART III.~~	~~No changes made.~~	Updated based on the changes made in PART III.
I The Medicine and What It Is Used For	~~Editorial updates to include Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg).~~	~~No changes made.~~	~~Editorial updates based on the PRAC comment included in the preliminary assessment~~

RMP Part/Module	~~RMP 9.1~~ ~~Major Changes~~	~~RMP 9.2~~ ~~Major Changes~~	RMP 10.0~~0~~1 ~~(9.3 + 9.4 +9.5)~~ Major Changes
II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks	~~Updated to lower the indication of Comirnaty original Omicron BA.4-5 from 5 years to 6 months of age and older.~~ ~~Updated based on the changes made in PART III and PART V.~~		~~report (X-0176) received 23 May 2023.~~ Editorial changes to include the new strain XBB.1.5. Updated based on the changes made in PART III and V.
ANNEXES TO THE RISK MANAGEMENT PLAN	~~Annex 2: Studies/milestones updated and addition of C4591051 and C4591052.~~ ~~Annex 3: Addition of studies C4591051 and C4591052.~~ ~~Annex 4: updated DCA versions.~~ ~~Annex 7: updated with results for phase 3 participants 12 to 15 years (Study C4591001, booster dose) and previous CT paediatric exposure from C4591007 moved in this Annex from Module SIII.~~ ~~Annex 8: Changes to reflect the updates.~~	~~Annex 2: Studies/milestones updated.~~ ~~Annex 8: Changes to reflect the updates.~~	Annex 2: removal of studies: C4591001, BNT-162-01 and WI235284 Annex 3: removal of studies: C4591001, BNT-162-01 and WI235284. ~~study C4591010.~~ ~~Annex 4: VAED/VAERD DCA removed.~~ Annex 8: Changes to reflect the updates.

Please note that only key parts of the RMP (Summary of Safety concerns, PV plan and RMM) are reflected below.

8.1. Summary of the safety concerns

No changes were made to the Summary of safety concerns.

Table 51: Summary of Safety Concerns

Important Identified Risks	Myocarditis and Pericarditis
Important Potential Risks	None
Missing Information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

8.2. Pharmacovigilance plan

Routine Pharmacovigilance Activities

Part III.1 Routine Pharmacovigilance Activities was updated to clean-up routine activities and remove PBS (Phosphate Buffered Saline) 30 mcg presentation from vial differentiation/ potential medication error.

Additional Pharmacovigilance Activities

Study BNT162-01 was completed and final CSR was submitted on 07 August 2023 (Procedure EMEA/H/C/005735/II/0187). Study BNT162-01 is an interventional EU safety study addressing Use in immunocompromised patients.

Study WI235284 was completed, and final CSR was submitted on 30 June 2023 (Procedure NEMEA/H/C/005735/II/0186/G). Study WI235284 is a US low-interventional effectiveness study addressing Vaccine effectiveness.

Study C4591001 was completed, and final CSR is submitted on 09 August 2023 (Procedure EMEA/H/C/005735/II/0188/G, i.e., this procedure). Study C4591001 is a global interventional safety study addressing Use in frail patients with comorbidities (C4591001 subset) and long term safety data.

Consequently, these studies have been removed from part III.2 Additional Pharmacovigilance Activities and part III.3 Summary Table of Ongoing and Planned Additional Pharmacovigilance Activities (not reproduced in this AR).

PRAC Rapporteur's Overall conclusions on the PhV Plan

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

8.3. Risk minimisation measures

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

PRAC Rapporteur's Overall conclusions on risk minimisation measures

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

8.4. Overall conclusion on the RMP

The MAH took the opportunity before the Opinion to update the version of the RMP to 11.0, and the sign off date to October 2023, as per the recommendations in the EMA guidance.

☒The changes to the RMP are acceptable.

9. Changes to the Product Information

As a result of this group of variations, section 4.8 of the SmPC are being updated to reflect data on booster dose administration into adolescent participants between 12 and 15 years of age.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.