EMA/134008/2022
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/005735/II/0093

Invented name: COMIRNATY

International non-proprietary name: tozinameran

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

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

Timetable	Date
Start of procedure	27 Dec 2021
CHMP Rapporteur Assessment Report	14 Jan 2022
CHMP members comments	24 Jan 2022
Updated CHMP Rapporteur Assessment Report	N/A
Request for Supplementary Information	27 Jan 2022
Re-start of procedure	07 Feb 2022
CHMP Rapporteur Assessment Report	15 Feb 2022
CHMP members comments	16 Feb 2022
ETF meeting	18 Feb 2022
Updated CHMP Rapporteur Assessment Report	18 Feb 2022
PDCO consultation	22 Feb 2022
CHMP Opinion	24 Feb 2022

Table of contents

1. Background information on the procedure 4

2. Introduction 4

3. Clinical Efficacy aspects 5

3.1. Methods – analysis of data submitted 5
3.1.1. Efficacy Endpoints and Analysis Methods in Study C4591031 5
3.1.2. Case Surveillance and Criteria 6
3.1.3. Efficacy Analysis Methods 6
3.2. Results 7
3.2.1. Relative Vaccine Efficacy from Booster Dose to 2 Months After Booster Dose 7
3.2.2. Relative Vaccine Efficacy from Booster Dose to Data Cut-off Date 8
3.2.3. Severe COVID-19 Cases from Booster Dose to Data Cut-off Date 21
3.3. Discussion 22

4. Clinical Safety aspects 23

4.1. Methods – analysis of data submitted 23
4.1.1. Disposition and Exposure 24
4.1.2. Demographics 28
4.2. Results 29
4.2.1. Local Reactions and Systemic Events 29
4.2.2. Adverse Events 29
4.3. Discussion 45

5. Changes to the Product Information 46

6. Request for supplementary information 47

6.1. Other concerns 47

7. Assessment of the responses to the request for supplementary information 47

7.1. Other concerns 47

8. Overall conclusion and impact on the benefit/risk balance 62

9. Recommendations 65

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 03 December 2021 an application for a variation.

The following changes were proposed:

Variation 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, IIIA and IIIB

Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update efficacy and safety information after booster dose, based on interim results from study C4591031, this is a randomized, placebo-controlled, phase 3 booster efficacy study involving participants ≥ 16 years of age who completed the primary series of BNT162b2 30 µg in Study C4591001. The Package Leaflet and Labelling are updated accordingly.

Moreover, the MAH was requested to consider whether data supports an extension of the approved use of a booster, to adolescents 16-18 (presently approved for adults).

In addition, the MAH took the opportunity to make minor editorial changes throughout the product information.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

2. Introduction

Phase 1/2/3 Study C4591001 is the registrational and pivotal study of the prophylactic BNT162b2 vaccine against COVID-19 in healthy individuals ≥12 years of age, that initiated in April 2020. In participants 16 years of age or older (for whom Comirnaty has been granted licensure), safety, tolerability, immunogenicity, and efficacy of BNT162b2 when administered as 2 doses of 30 µg given approximately 21 days apart has been reported across the final analysis (03 December 2020) and 6-month update (29 April 2021) interim CSRs; additionally, the safety and immunogenicity of participants 18-55 years of age was reported in the Study C4591001 booster (Dose 3) interim CSR (23 August 2021).

The booster dose (third dose) of BNT162b2 (30 µg), administered at approximately 6 months after Dose 2 for individuals ≥18 years of age was approved on 05 October 2021 in the EU. This decision was based on the data on immunogenicity and safety for a group (N= 268) of Phase 3 participants in Study C4591001, who received a booster dose.

Study C4591031 is a continuation study of the pivotal C4591001 study. Study C4591031 is the ongoing, randomized, placebo-controlled, Phase 3 booster efficacy study. The present submission includes interim analysis of relative vaccine efficacy and safety from Study C4591031.

Approximately 10,000 individuals ≥16 years of age randomized 1:1 to receive a booster dose of BNT162b2 30 µg or placebo at least 6 months after completing the 2-dose primary series in Study C4591001 and followed up to at least 2 months post-booster. Randomization was stratified by age, such that approximately 60% of participants enrolled would be ≥16 to 55 years of age and approximately 40% of participants would be >55 years of age. Assessments include safety evaluations and COVID-19 case

surveillance for booster efficacy estimation after the booster dose. This study was conducted at 123 sites. The majority of sites was in the US (117), but also sites in Brazil (2) and South Africa (4) participated.

The protocol for this substudy is part of the master protocol for Study C4591031 to evaluate the safety, and/or immunogenicity, and/or efficacy of various BNT162b2 boosting strategies across different populations of participants (e.g., age groups) who previously received 2 doses of BNT162b2.

This C4591031 2-month interim report for Substudy A includes the following analyses:

- Efficacy analyses of a single booster dose of BNT162b2 30 µg from 7 days after booster dose to 2 months after booster dose and to the data cut-off date (05 October 2021).
- Safety analysis of a single booster dose of BNT162b2 30 µg from booster dose to 1 month after booster dose and to the data cut-off date (05 October 2021).

Other objectives in Substudy A of Study C4591031 (Section 2) will be reported by the MAH at a later time.

Unblinding Considerations

It had originally been intended that all participants would remain blinded until the outcome of the protocol prespecified data analysis that was planned to be conducted once all participants reached 2 months after booster vaccination had been reviewed by the Data Monitoring Committee (DMC). However, in light of the observation of waning effectiveness and recommendation for booster doses in some countries, per the protocol, participants could be unblinded from 24 September 2021 onwards, and those who had been randomized to receive Dose 3 of placebo were offered a dose of BNT162b2 30 µg in order to receive a booster of active vaccine. At the time of this analysis, some (but not all) participants have been unblinded per protocol; the analyses take account of this, as individual participant data are censored at the time of their unblinding.

3. Clinical Efficacy aspects

3.1. Methods – analysis of data submitted

3.1.1. Efficacy Endpoints and Analysis Methods in Study C4591031

Efficacy analyses were conducted based on the evaluable and all-available (modified intent-to-treat [mITT]) efficacy populations. Case criteria and summary of efficacy analysis methods are provided below for reference.

Vaccine efficacy (VE) was evaluated as follows:

- **Primary efficacy endpoint**: confirmed COVID-19 incidence from 7 days after the booster dose per 1000 person-years of blinded follow-up in participants without or with or without evidence of prior SARS-CoV-2 infection up to 7 days after booster vaccination.
- **Secondary efficacy endpoint**: COVID-19: confirmed severe COVID-19 incidence from 7 days after booster vaccination per 1000 person-years of blinded follow-up.

Evaluable cases were those confirmed with a positive PCR result for SARS-CoV-2 from a nasal (midturbinate) swab, plus one or more of the symptoms specified in the case criteria below that triggered a study illness visit. Case evaluation was based on results from the central laboratory using a validated RT-PCR test (Cepheid; FDA-approved under EUA and Pfizer-validated), or other equivalent nucleic acid

amplification–based test (i.e., NAAT) to detect SARS-CoV-2; the result could be from a local laboratory if the test was prespecified as acceptable per protocol.

Definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, were considered as follows; for both, the onset date of the case was the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they were considered as part of a single illness.

3.1.2. Case Surveillance and Criteria

Confirmed COVID-19: Presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrhea
- Vomiting

Confirmed severe COVID-19 (FDA definition[i]): Confirmed COVID-19 and at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness:
  - respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg

- Respiratory failure defined as needing:
  - high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO

- Evidence of shock: SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors

- Significant acute renal, hepatic, or neurologic dysfunction

- Admission to an intensive care unit (ICU)

- Death

Confirmed severe COVID-19 (CDC definition[ii]): Confirmed COVID-19 and at least 1 of the following: hospitalization, admission to the ICU, intubation or mechanical ventilation, or death.

3.1.3. Efficacy Analysis Methods

Descriptive efficacy analyses were conducted based on the evaluable and all-available (modified intent-to-treat [mITT]) efficacy populations. Relative vaccine efficacy (RVE) was estimated in participants without prior evidence of SARS-CoV-2 infection before or during the vaccine or booster vaccine regimen, and those with or without prior evidence of SARS-CoV-2 infection. All participants had previously received the primary series of BNT162b2 30 µg, therefore RVE compares a third dose of active vaccine (third dose following the two-dose primary series) versus placebo (no third dose following the two-dose primary series).

The RVE against confirmed COVID-19 from 7 days after booster vaccination was estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of blinded follow-up in the active vaccine booster group to the corresponding illness rate in the placebo booster group. RVE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time are included with efficacy analyses. Missing efficacy data (ie, where symptom was present without laboratory testing data) were not imputed. Kaplan-Meier cumulative incidence curves were provided.

Subgroup analyses of RVE were conducted based on demographics (age group, sex, race, and ethnicity), country, dose interval between Dose 2 and booster dose, baseline SARS-CoV-2 status, and risk status based on Charlson Comorbidity Index or a body mass index (BMI) ≥30 kg/m^2.

In addition to analyses of RVE (performed only for all cases per FDA definition adopted in the protocol), descriptive statistics (counts, percentages, and the associated Clopper-Pearson 95% CIs) were provided for severe COVID-19 cases as defined by FDA and as defined by CDC, if sufficient severe cases accrued to support such an analysis.

The protocol prespecified interim analysis of efficacy was conducted when all participants reached 2 months post-booster, for a planned DMC review. The interim analysis for DMC review included COVID-19 cases that occurred from 7 days after booster vaccination up to 2 months after booster vaccination. The timing of interim analyses was prespecified in the protocol in order to assess whether those in the placebo group were potentially disadvantaged by not having received a BNT162b2 booster dose.

Subsequent to the DMC review of cases analysed up to 2 months post-booster, the interim efficacy analysis was updated to include evaluation of all COVID-19 cases accrued up to the data cutoff date of 05 October 2021 (i.e., not limited to case accrual up to 2 months of follow-up post-booster). These data encompass the period of placebo-controlled blinded follow-up through the data cutoff date, which represents a median of 2.5 months post-booster follow-up.

3.2. Results

3.2.1. Relative Vaccine Efficacy from Booster Dose to 2 Months After Booster Dose

The protocol prespecified interim analysis for DMC review included COVID-19 cases occurring from 7 days after booster vaccination up to 2 months after booster vaccination, timed in order to assess whether those in the placebo group were potentially disadvantaged by not having received a BNT162b2 booster dose. Results from booster vaccination to 2 months post-booster included:

- Among participants without evidence of infection prior to 7 days after booster vaccination in the evaluable efficacy population, based on the first COVID-19 occurrence from ≥7 days after booster vaccination to <2 months after booster vaccination, the RVE was estimated as 95.6% (2-sided 95% CI: 89.3%, 98.6%), based on 5 cases in the BNT162b2 group and 109 cases in the placebo group.
- Among participants with or without evidence of infection prior to 7 days after booster vaccination in the evaluable efficacy population, based on the first COVID-19 occurrence from ≥7 days after booster vaccination to <2 months after booster vaccination, the estimated RVE was 94.7% (2-sided 95% CI: 88.2%, 98.1%), based on 6 cases in the BNT162b2 group and 110 cases in the placebo group.

Based on these results showing high RVE at 2 months post-booster, the DMC recommended unblinding the study and continuation of participants being unblinded to allow placebo recipients the opportunity to receive a BNT162b2 booster dose. The interim analysis was then updated including all cases accrued up to the data cut-off date of 05 October 2021, as summarized below.

3.2.2. Relative Vaccine Efficacy from Booster Dose to Data Cut-off Date

3.2.2.1. Efficacy Populations

The efficacy populations are presented in Table 1. In total, 11 participants (0.1%) were excluded from the all-available efficacy population as they did not receive the study intervention (booster dose).

The evaluable efficacy population include 98.6% of participants in both the BNT162b2 and placebo groups. Participants without evidence of prior SARS-CoV-2 infection prior to 7 days post-booster were balanced between groups with 4714 participants (92.6%) in the BNT162b2 group and 4692 participants (92.9%) in the placebo group.

In total, 142 participants (1.4%) were excluded from the evaluable efficacy population, due to having important protocol deviations on or prior to 7 days after booster vaccination (1.3%), not meeting all eligibility criteria after randomization into the booster study (1.2%), or not receiving vaccine as randomized (0.1%). There was no imbalance across the groups in the exclusions.

Table 1. Efficacy Populations – Blinded Follow-up Period

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	5088 (100.0)	5048 (100.0)	10136 (100.0)
All-available efficacy population	5082 (99.9)	5043 (99.9)	10125 (99.9)
Participants without evidence of infection before booster vaccination	4790 (94.1)	4774 (94.6)	9564 (94.4)
Participants excluded from the all-available efficacy population	6 (0.1)	5 (0.1)	11 (0.1)
Reason for exclusion			
Did not receive vaccination	6 (0.1)	5 (0.1)	11 (0.1)
Evaluable efficacy population	5018 (98.6)	4976 (98.6)	9994 (98.6)
Participants without evidence of infection prior to 7 days after booster vaccination	4714 (92.6)	4692 (92.9)	9406 (92.8)
Participants excluded from evaluable efficacy population	70 (1.4)	72 (1.4)	142 (1.4)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	61 (1.2)	60 (1.2)	121 (1.2)
Did not receive vaccination as randomized	7 (0.1)	5 (0.1)	12 (0.1)
Had other important protocol deviations on or prior to 7 days after booster vaccination	64 (1.3)	64 (1.3)	128 (1.3)

Table 1. Efficacy Populations – Blinded Follow-up Period

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)

Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but not included in the analyses of the overall study objectives.
a. n = Number of participants with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Participants may have been excluded for more than 1 reason.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adsl Table Generation: 15OCT2021 (14:44)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adsl_eff_pop

3.2.2.2. Duration of Follow-Up

As of the data cut-off date (05 October 2021), the median duration of blinded follow-up after receipt of the booster dose for the evaluable efficacy population without evidence of prior infection with SARS-CoV-2 prior to 7 days post-booster was 2.5 months (Table 2). Most participants (97.0%) had ≥2 to <4 months of follow-up post-booster.

The median follow-up time for this population was similar to that for the safety population. The duration of follow-up time for the evaluable efficacy population with or without evidence of prior SARS-CoV-2 infection prior to 7 days post-booster was similar.

Table 2. Follow-up Time After Booster Vaccination – Blinded Follow-up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=4714) n[b] (%)	Placebo (N[a]=4692) n[b] (%)	Total (N[a]=9406) n[b] (%)
Participants (%) with length of follow-up of:			
Blinded follow-up period			
<2 Months	94 (2.0)	188 (4.0)	282 (3.0)
≥2 Months to <4 months	4620 (98.0)	4504 (96.0)	9124 (97.0)
Mean (SD)	2.6 (0.29)	2.5 (0.34)	2.5 (0.32)
Median	2.5	2.5	2.5
Min, max	(0.4, 3.5)	(0.3, 3.5)	(0.3, 3.5)

Table 2. Follow-up Time After Booster Vaccination – Blinded Follow-up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=4714) n[b] (%)	Placebo (N[a]=4692) n[b] (%)	Total (N[a]=9406) n[b] (%)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis.
Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but not included in the analyses of the overall study objectives.
Note: Follow-up time was calculated from booster vaccination to the cutoff date or withdrawal date or the day before date of unblinding (per protocol) or the day before date of receiving COVID-19 vaccine off study, whichever date was earlier.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adsl Table Generation: 16OCT2021 (02:37) (Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adsl_fu_d2_wo_eval

3.2.2.3. Demographics

Most participants in the evaluable efficacy population of participants without evidence of SARS-CoV-2 infection prior to 7 days post-booster were White (80.1%), with 8.0% Black or African American participants, 5.7% Asian participants, 3.9% multiracial participants, and other racial groups comprising <2% (Table 3). There were 14.6% Hispanic/Latino participants. The median age at the time of study vaccination was 53.0 years, and 49.4% of participants were male. Most study participants (87.0%) were enrolled in the US.

The younger age group (16 to 55 years of age) made up 54.8% of the population; this included 78 participants (0.8%) who were 16 to 17 years of age. The older age group (>55 years of age) made up 45.2% of the population; this included 2238 participants (23.8%) who were ≥65 years of age.

Obese participants made up 35.4% of the population. Baseline comorbidities (including Charlson comorbidities and obesity, which increase an individual's risk of developing severe COVID-19) were reported by 4557 participants (48.4%) in the population and were balanced across the BNT162b2 and placebo groups.

The evaluable efficacy population of participants without evidence of SARS-CoV-2 infection prior to 7 days post-booster had demographics similar to those reported for the safety population. The demographics in the evaluable efficacy population including participants with or without evidence of SARS-CoV-2 infection prior to 7 days post-booster and the all-available efficacy populations were also similar.

Table 3. Demographic Characteristics – Blinded Follow-up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=4714) n[b] (%)	Placebo (N[a]=4692) n[b] (%)	Total (N[a]=9406) n[b] (%)
Sex			
Male	2294 (48.7)	2356 (50.2)	4650 (49.4)
Female	2420 (51.3)	2336 (49.8)	4756 (50.6)
Race			
White	3769 (80.0)	3766 (80.3)	7535 (80.1)
Black or African American	372 (7.9)	378 (8.1)	750 (8.0)
American Indian or Alaska Native	82 (1.7)	88 (1.9)	170 (1.8)
Asian	274 (5.8)	258 (5.5)	532 (5.7)
Native Hawaiian or other Pacific Islander	7 (0.1)	11 (0.2)	18 (0.2)
Multiracial	188 (4.0)	177 (3.8)	365 (3.9)
Not reported	22 (0.5)	14 (0.3)	36 (0.4)
Ethnicity			
Hispanic/Latino	690 (14.6)	686 (14.6)	1376 (14.6)
Non-Hispanic/non-Latino	4014 (85.2)	3998 (85.2)	8012 (85.2)
Not reported	10 (0.2)	8 (0.2)	18 (0.2)
Country			
Brazil	519 (11.0)	528 (11.3)	1047 (11.1)
South Africa	79 (1.7)	97 (2.1)	176 (1.9)
USA	4116 (87.3)	4067 (86.7)	8183 (87.0)
Age group (years)			
16-55	2584 (54.8)	2572 (54.8)	5156 (54.8)
>55	2130 (45.2)	2120 (45.2)	4250 (45.2)
≥65	1120 (23.8)	1118 (23.8)	2238 (23.8)
16-17	41 (0.9)	37 (0.8)	78 (0.8)
16-25	223 (4.7)	249 (5.3)	472 (5.0)
16-30	460 (9.8)	473 (10.1)	933 (9.9)
18-30	419 (8.9)	436 (9.3)	855 (9.1)
31-40	722 (15.3)	692 (14.7)	1414 (15.0)
16-40	1182 (25.1)	1165 (24.8)	2347 (25.0)
41-50	889 (18.9)	922 (19.7)	1811 (19.3)
51-60	1049 (22.3)	1012 (21.6)	2061 (21.9)
>60	1594 (33.8)	1593 (34.0)	3187 (33.9)
16-64	3594 (76.2)	3574 (76.2)	7168 (76.2)
18-64	3553 (75.4)	3537 (75.4)	7090 (75.4)
55-64	1129 (23.9)	1088 (23.2)	2217 (23.6)
65-74	869 (18.4)	872 (18.6)	1741 (18.5)
≥75	251 (5.3)	246 (5.2)	497 (5.3)
75-85	250 (5.3)	243 (5.2)	493 (5.2)
>85	1 (0.0)	3 (0.1)	4 (0.0)
Age at vaccination (years)			
Mean (SD)	52.1 (15.20)	52.0 (15.25)	52.0 (15.22)

Table 3. Demographic Characteristics – Blinded Follow-up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=4714) n[b] (%)	**Placebo (N[a]=4692) n[b] (%)**	**Total (N[a]=9406) n[b] (%)**
Median	53.0	53.0	53.0
Min, max	(16, 86)	(16, 87)	(16, 87)
Comorbidities[c]			
Yes	2272 (48.2)	2285 (48.7)	4557 (48.4)
No	2442 (51.8)	2407 (51.3)	4849 (51.6)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	53 (1.1)	45 (1.0)	98 (1.0)
Normal weight (≥18.5-24.9 kg/m^2)	1338 (28.4)	1367 (29.1)	2705 (28.8)
Overweight (≥25.0-29.9 kg/m^2)	1660 (35.2)	1608 (34.3)	3268 (34.7)
Obese (≥30.0 kg/m^2)	1661 (35.2)	1672 (35.6)	3333 (35.4)
Missing	2 (0.0)	0	2 (0.0)

Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 Charlson Comorbidity Index category or a BMI ≥30 kg/m^2.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adsl Table Generation: 22OCT2021 (09:14) (Data Cut-off Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adsl_demo_7d_eval_eff_new

Up to the data cut-off date (05 October 2021), the RVE in the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days post-booster was observed as 95.3% (2-sided 95% CI: 89.5%, 98.3%), based on 6 cases in the BNT162b2 group and 123 cases in the placebo group confirmed from at least 7 days after the booster dose (Table 4).

RVE in the evaluable efficacy population with or without evidence of SARS-CoV-2 infection prior to 7 days post-booster was observed as 94.6% (2-sided 95% CI: 88.5%, 97.9%), based on 7 cases in the BNT162b2 group and 124 cases in the placebo group confirmed from at least 7 days after the booster dose (Table 4).

Table 4: Vaccine efficacy – First COVID-19 occurrence from 7 days after booster vaccination – participants 16 years of age and older without evidence of infection and participants with or without evidence of infection prior to 7 days after booster vaccination – evaluable efficacy population

First COVID-19 occurrence from 7 days after booster dose in participants <u>without</u> evidence of prior SARS-CoV-2 infection*			
	Comirnaty Na=4695 Cases n1b Surveillance Timec (n2d)	**Placebo Na=4671 Cases n1b Surveillance Timec (n2d)**	**Relative Vaccine Efficacye % (95% CIf)**
First COVID-19 occurrence from 7 days after booster vaccination	6 0.823 (4659)	123 0.792 (4614)	95.3 (89.5, 98.3)
First COVID-19 occurrence from 7 days after booster dose in participants <u>with or without</u> evidence of prior SARS-CoV-2 infection			
	Comirnaty Na=4993 Cases n1b Surveillance Timec (n2d)	**Placebo Na=4952 Cases n1b Surveillance Timec (n2d)**	**Relative Vaccine Efficacye % (95% CIf)**
First COVID-19 occurrence from 7 days after booster vaccination	7 0.871 (4934)	124 0.835 (4863)	94.6 (88.5, 97.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non-booster).
f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

3.2.2.4. All-Available Efficacy Population

In the all-available efficacy (mITT) population, the observed RVE from booster vaccination onwards (up to the data cut-off date of 05 October 2021), was 89.8% (2-sided 95% CI: 82.6%, 94.4%), based on 15 cases in the BNT162b2 group and 141 cases in the placebo group reported after booster vaccination (Table 5).

From the time of booster vaccination up to <7 days post-booster, the observed RVE was 47.3% (2-sided 95% CI: -32.3%, 80.7%), based on 8 cases in the BNT162b2 and 15 cases in the placebo group during this period. From ≥7 days to <2 months post-booster, the observed RVE was 94.8% (2-sided 95% CI: 88.4%, 98.1%), with 6 cases in the BNT162b2 group and 112 cases in the placebo group during this period. The observed RVE at ≥2 to <4 months post-booster was 93.3% (2-sided 95% CI: 56.1%, 99.8%), with 1 case in the BNT162b2 group and 14 cases in the placebo group during this period.

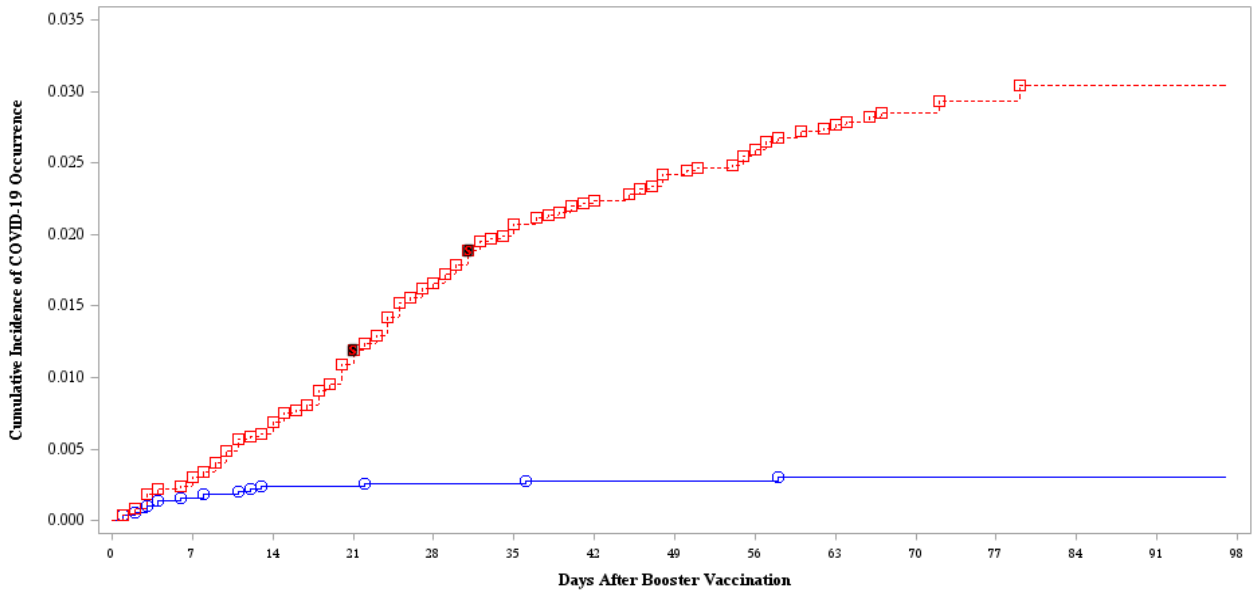
The Kaplan-Meier curves from booster vaccination onwards show a steady and steep accumulation of confirmed COVID-19 cases in the placebo group including 2 severe cases denoted in with 'S' on the placebo curve (severe cases are discussed further in section 3.2.3.), compared with a relatively flat curve for the BNT162b2 group in which few cases accrued and no severe cases were reported (Figure 1).

Table 5. Vaccine Efficacy – First COVID-19 Occurrence After Booster Vaccination – Blinded Follow-up Period – All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=5056)		Placebo (N[a]=5019)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	RVE (%)	(95% CI[e])
First COVID-19 occurrence after booster vaccination	15	0.978 (5003)	141	0.940 (4943)	89.8	(82.6, 94.4)
Booster vaccination to 7 days after booster vaccination	8	0.096 (5003)	15	0.095 (4943)	47.3	(-32.3, 80.7)
≥7 Days after booster vaccination to <2 months after booster vaccination	6	0.668 (4995)	112	0.645 (4928)	94.8	(88.4, 98.1)
≥2 Months after booster vaccination to <4 months after booster vaccination	1	0.214 (4891)	14	0.200 (4616)	93.3	(56.1, 99.8)

Abbreviation: RVE = relative vaccine efficacy of the BNT162b2 booster group relative to the placebo group (nonbooster).
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from the booster vaccination to the end of the surveillance period for the overall row and from the start to the end of the range stated for each time interval.
d. n2 = Number of participants at risk for the endpoint.
e. 2-Sided CI for RVE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adc19ef Table Generation: 15OCT2021 (15:18) (Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adc19ef_ve_cov_aai

Figure 1. Cumulative Incidence Curves – First COVID-19 Occurrence After Booster Vaccination – Blinded Follow-up Period – All Available Efficacy Population



Participants at Risk

A:	5003	4995	4990	4990	4988	4978	4975	4968	4917	4338	3053	1632	236	8	0
B:	4943	4931	4910	4869	4827	4780	4754	4735	4645	4082	2851	1482	204	6	0

Cumulative Number of Events

A:	0	8	12	12	13	13	14	14	14	15	15	15	15	15	15
B:	0	15	34	59	82	102	110	119	127	135	138	140	141	141	141

Note: "S" indicates participants with severe COVID-19.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adc19ef Table Generation: 15OCT2021 (15:48)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: /nda2_ubBIA/C4591031_A_IA_1/adc19ef_f001_km_aai

3.2.2.5. Signs and Symptoms of COVID-19

Based on cases up to the data cut-off date (05 October 2021), signs and symptoms associated with cases confirmed ≥7 days post-booster in the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days post-booster suggest that the 6 cases in the BNT162b2 group were overall milder than the 123 cases in the placebo group (Table 6).

All of the cases in the BNT162b2 group were associated with ≤3 signs or symptoms, which notably excluded any fevers, new or increased shortness of breath, or new or increased muscle pain. Cases in the placebo group were associated with a greater number of reported signs and symptoms, including 31.7% of participants with ≥4 signs or symptoms. These included fever in 43.9% of cases, new or increased muscle pain in 44.7% of cases, and new or increased shortness of breath in 11.4% of cases.

The overall profiles and patterns of signs and symptoms associated with the evaluable efficacy population with or without evidence of SARS-CoV-2 infection prior to 7 days post-booster, as well as the all-available efficacy population, were similar; fever and shortness of breath were rarely reported for cases in the BNT162b2 group.

Table 6. Signs and Symptoms for First COVID-19 Occurrence From 7 Days After Booster Vaccination – Blinded Follow-up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

	Vaccine Group (as Randomized)		
Signs and Symptoms	**BNT162b2 (30 µg) (N[a]=6) n[b](%)**	**Placebo (N[a]=123) n[b](%)**	**Total (N[a]=129) n[b](%)**
Participants with specific signs and symptoms of COVID-19			
Fever	0 (0.0)	54 (43.9)	54 (41.9)
New or increased cough	1 (16.7)	89 (72.4)	90 (69.8)
New or increased shortness of breath	0 (0.0)	14 (11.4)	14 (10.9)
Chills	2 (33.3)	47 (38.2)	49 (38.0)
New or increased muscle pain	0 (0.0)	55 (44.7)	55 (42.6)
New loss of taste or smell	1 (16.7)	42 (34.1)	43 (33.3)
Sore throat	3 (50.0)	48 (39.0)	51 (39.5)
Diarrhea	2 (33.3)	20 (16.3)	22 (17.1)
Vomiting	1 (16.7)	1 (0.8)	2 (1.6)
Participants with specific number of signs and symptoms			
1	3 (50.0)	31 (25.2)	34 (26.4)
2	2 (33.3)	22 (17.9)	24 (18.6)
3	1 (16.7)	31 (25.2)	32 (24.8)
4	0 (0.0)	11 (8.9)	11 (8.5)
5	0 (0.0)	16 (13.0)	16 (12.4)
>5	0 (0.0)	12 (9.8)	12 (9.3)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after the booster vaccination) were included in the analysis.
a. N = number of participants with a first COVID-19 occurrence from 7 days after the booster vaccination in the specified group. This value is used as the denominator for the percentage calculations.
b. n = Number of participants with the specific criteria meeting the COVID-19 case definition. A participant can have more than 1 symptom.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adc19ef Table Generation: 15OCT2021 (15:18) (Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adsympt_symp_cov_7d_wo_eval

3.2.2.6. Subgroup Analyses

Based on cases up to the data cut-off date (05 October 2021), subgroup analyses were conducted to estimate the RVE for the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days post-booster, based on demographics and baseline characteristics of geography and time to booster (Table 7), as well as risk factors (Table 8) including specific high-risk comorbidities (Table 9). For all subgroups, the confirmed COVID-19 cases were predominantly reported in the placebo group.

The subgroup analysis results for estimated RVE for the evaluable efficacy population with or without evidence of SARS-CoV-2 infection prior to 7 days post-booster, as well as the all-available efficacy population, were similar.

Participants who were baseline SARS-CoV-2 positive included only 1 participant each in the BNT162b2 and placebo groups with confirmed COVID-19 cases as of the data cut-off date, precluding meaningful analysis by baseline status.

Demographics and Baseline Characteristics

Subgroup analyses by demographic and baseline characteristics are shown in Table 7.

Age

All ages analysed showed similarly high observed RVE; all were estimated to be >90%. Several ages in the analysis included small numbers of cases and participants which contributed to wide confidence intervals around the point estimate (i.e., 16 to 17 years, ≥75 years, and 75 to 85 years of age).

Sex

The *observed* RVE was high for both sexes: 94.3% (2-sided 95% CI: 84.8%, 98.5%) for male participants and 96.5% (2-sided 95% CI: 86.7%, 99.6%) for female participants.

Race

The observed RVE was high for most race subgroups; all were estimated to be >95%, with the exception of Asian participants (69.4% with 2-sided 95% CI: -280.7%, 99.4%). Other than White and Black or African American, most race subgroups included a limited numbers of cases and participants which contributed to wide confidence intervals around the point estimates.

Ethnicity

The observed RVE was high for both ethnic groups: 94.8% (2-sided 95% CI: 67.5%, 99.9%) for Hispanic/Latino participants and 95.4% (2-sided 95% CI: 88.9%, 98.5%) for non-Hispanic/non-Latino participants.

Country

Analysis of cases reported in all countries (US, South Africa, and Brazil) showed similarly high observed RVE; all were estimated to be >95%. South Africa and Brazil included small numbers of cases and participants which contributed to wide confidence intervals around the point estimates.

Time to Booster

Analysis of RVE by time intervals between receipt of Dose 2 to receipt of the booster dose showed similarly high observed RVE; all were estimated to be >90%. These intervals ranged from ≥6 to <8 months up to >12 months after Dose 2 until receipt of booster vaccination. A limited number of participants received their booster dose >12 months after Dose 2, which contributed to wide confidence intervals around the point estimate.

Risk Status

Subgroup analyses by risk status are shown in Table 8, and for specific high-risk comorbidities in Table 9.

Risk Status

All risk status groups analysed including those at-risk, obese, and with combinations of high-risk age and risk status showed similarly high observed RVE; all were estimated to be >90%, with the exception of individuals ≥65 years of age and at risk (76.5%). Several risk groups in the analysis included small numbers of cases and participants which contributed to wide confidence intervals around the point estimate (ie, ≥65 years of age and at risk, ≥65 years of age and obese).

Comorbidity

Specific high-risk comorbidities analysed showed similarly high observed RVE; all were estimated to be >91%, with the exceptions of malignancy (78.6%) and cardiovascular disease (-57.3%). These two comorbidity groups included a small number of participants which contributed to wide confidence intervals around the point estimate. The cardiovascular comorbidity group in particular had a very small number of cases and participants including 2 in the BNT162b2 group and 1 in the placebo group, which precludes a precise estimation of RVE.

Table 7. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Booster Vaccination, by Subgroup – Blinded Follow-up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=4695)		Placebo (N[a]=4671)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	RVE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after booster vaccination						
Overall	6	0.823 (4659)	123	0.792 (4614)	95.3	(89.5, 98.3)
Age group (years)						
16-55	3	0.446 (2548)	81	0.427 (2523)	96.5	(89.3, 99.3)
>55	3	0.378 (2111)	42	0.365 (2091)	93.1	(78.4, 98.6)
≥65	1	0.198 (1112)	13	0.192 (1106)	92.5	(50.3, 99.8)
16-17	0	0.007 (41)	2	0.006 (37)	100.0	(-348.6, 100.0)
16-25	0	0.039 (223)	7	0.041 (245)	100.0	(26.4, 100.0)
16-30	0	0.080 (457)	11	0.079 (466)	100.0	(60.5, 100.0)
18-30	0	0.073 (416)	9	0.073 (429)	100.0	(49.1, 100.0)
31-40	0	0.124 (711)	31	0.115 (682)	100.0	(88.3, 100.0)
16-40	0	0.204 (1168)	42	0.194 (1148)	100.0	(91.3, 100.0)
41-50	2	0.152 (876)	21	0.153 (901)	90.5	(60.9, 98.9)
51-60	2	0.185 (1034)	36	0.170 (990)	94.9	(80.1, 99.4)
>60	2	0.282 (1581)	24	0.275 (1575)	91.9	(67.3, 99.1)
16-64	5	0.625 (3547)	110	0.600 (3508)	95.6	(89.5, 98.6)
18-64	5	0.618 (3506)	108	0.594 (3471)	95.6	(89.3, 98.6)
55-64	3	0.201 (1116)	31	0.187 (1068)	91.0	(71.1, 98.2)
65-74	1	0.153 (863)	12	0.149 (865)	91.9	(45.1, 99.8)
≥75	0	0.045 (249)	1	0.042 (241)	100.0	(-3607.9, 100.0)
75-85	0	0.045 (248)	1	0.042 (238)	100.0	(-3577.6, 100.0)
Sex						
Male	4	0.398 (2258)	70	0.396 (2310)	94.3	(84.8, 98.5)
Female	2	0.425 (2401)	53	0.396 (2304)	96.5	(86.7, 99.6)
Race						

Table 7. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Booster Vaccination, by Subgroup – Blinded Follow-up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=4695)		Placebo (N[a]=4671)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	RVE (%)	(95% CI[e])
White	5	0.661 (3727)	100	0.638 (3709)	95.2	(88.4, 98.5)
Black or African American	0	0.064 (363)	13	0.063 (364)	100.0	(68.0, 100.0)
American Indian or Alaska Native	0	0.013 (80)	4	0.013 (86)	100.0	(-59.2, 100.0)
Asian	1	0.046 (272)	3	0.043 (255)	69.4	(-280.7, 99.4)
Multiracial	0	0.034 (188)	2	0.031 (175)	100.0	(-395.3, 100.0)
Not reported	0	0.004 (22)	1	0.002 (14)	100.0	(-2233.3, 100.0)
Ethnicity						
Hispanic/Latino	1	0.118 (683)	19	0.116 (683)	94.8	(67.5, 99.9)
Non-Hispanic/non-Latino	5	0.704 (3967)	104	0.675 (3923)	95.4	(88.9, 98.5)
Country						
Brazil	0	0.092 (518)	4	0.093 (526)	100.0	(-52.7, 100.0)
South Africa	0	0.012 (74)	2	0.015 (93)	100.0	(-554.9, 100.0)
USA	6	0.719 (4067)	117	0.684 (3995)	95.1	(89.1, 98.2)
Time between Dose 2 and booster vaccination						
≥6 - <8 months after Dose 2	1	0.115 (698)	10	0.109 (676)	90.5	(33.4, 99.8)
≥8 - <10 months after Dose 2	1	0.132 (738)	26	0.128 (741)	96.3	(77.3, 99.9)
≥10 - <12 months after Dose 2	4	0.550 (3058)	82	0.531 (3037)	95.3	(87.5, 98.7)
≥12 months after Dose 2	0	0.027 (165)	5	0.024 (160)	100.0	(-0.2, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; RVE = relative vaccine efficacy of the BNT162b2 booster group relative to the placebo group (nonbooster); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis.

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. 2-Sided CI for RVE is derived based on the Clopper and Pearson method adjusted for surveillance time.

PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adc19ef Table Generation: 22OCT2021 (09:13) (Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adc19ef_ve_cov_7d_wo_sg_eval_new

Table 8. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Booster Vaccination, by Risk Status – Blinded Follow-up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=4695)		Placebo (N[a]=4671)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	RVE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after booster vaccination						
Overall	6	0.823 (4659)	123	0.792 (4614)	95.3	(89.5, 98.3)
At risk[f]						
Yes	5	0.394 (2233)	64	0.385 (2231)	92.4	(81.2, 97.6)
No	1	0.429 (2426)	59	0.406 (2383)	98.4	(90.7, 100.0)
Age group (years) and at risk status						
16-64 and not at risk	1	0.344 (1949)	50	0.321 (1885)	98.1	(89.1, 100.0)
16-64 and at risk	4	0.281 (1598)	60	0.279 (1623)	93.4	(82.2, 98.3)
≥65 and not at risk	0	0.085 (477)	9	0.085 (498)	100.0	(48.9, 100.0)
≥65 and at risk	1	0.113 (635)	4	0.107 (608)	76.5	(-137.5, 99.5)
Obese[g]						
Yes	2	0.289 (1634)	52	0.283 (1637)	96.2	(85.7, 99.6)
No	4	0.533 (3023)	71	0.508 (2977)	94.6	(85.6, 98.6)
Age group (years) and obesity status						
16-64 and not obese	3	0.403 (2284)	61	0.381 (2234)	95.3	(85.8, 99.1)
16-64 and obese	2	0.222 (1262)	49	0.219 (1274)	96.0	(84.7, 99.5)
≥65 and not obese	1	0.131 (739)	10	0.128 (743)	90.2	(31.4, 99.8)
≥65 and obese	0	0.067 (372)	3	0.064 (363)	100.0	(-132.4, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test;
RVE = relative vaccine efficacy of the BNT162b2 booster group relative to the placebo group (nonbooster);
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection
(ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT
[nasal swab] at any unscheduled visit prior to 7 days after the booster vaccination) were included in the analysis.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. 2-Sided CI for RVE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Includes participants who had at least 1 Charlson Comorbidity Index category or a BMI ≥30 kg/m^2.
g. Participants who had a BMI ≥30 kg/m^2.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adc19ef Table Generation: 15OCT2021 (15:21) (Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adc19ef_ve_cov_7d_wo_rg_eval

Table 9. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Booster Vaccination, by Comorbidity Status – Blinded Follow-up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=4695)		Placebo (N[a]=4671)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	RVE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after booster vaccination						
Overall	6	0.823 (4659)	123	0.792 (4614)	95.3	(89.5, 98.3)
Comorbidity						
No comorbidity	1	0.429 (2426)	59	0.406 (2383)	98.4	(90.7, 100.0)
Any comorbidity[f]	5	0.394 (2233)	64	0.385 (2231)	92.4	(81.2, 97.6)
Any malignancy	1	0.044 (247)	4	0.037 (214)	78.6	(-116.4, 99.6)
Cardiovascular	2	0.030 (169)	1	0.023 (133)	-57.3	(-9181.8, 91.8)
Chronic pulmonary disease	1	0.071 (404)	16	0.074 (437)	93.4	(57.8, 99.8)
Diabetes	1	0.068 (386)	17	0.066 (384)	94.3	(63.3, 99.9)
Obese (≥30.0 kg/m^2)	2	0.289 (1634)	52	0.283 (1637)	96.2	(85.7, 99.6)
Hypertension	3	0.226 (1266)	33	0.221 (1265)	91.1	(71.7, 98.3)
Diabetes (including gestational diabetes)	1	0.068 (389)	17	0.067 (387)	94.3	(63.3, 99.9)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test;
RVE = relative vaccine efficacy of the BNT162b2 booster group relative to the placebo group (nonbooster);
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection
(ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT
[nasal swab] at any unscheduled visit prior to 7 days after the booster vaccination) were included in the analysis.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. 2-Sided CI for RVE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Participant who had 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 Charlson Comorbidity Index category or a BMI ≥30 kg/m2.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adc19ef Table Generation: 15OCT2021 (15:21) (Data cut-off Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adc19ef_ve_cov_7d_wo_cg_eval

3.2.3. Severe COVID-19 Cases from Booster Dose to Data Cut-off Date

Based on cases up to the data cut-off date (05 October 2021), in the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days post-booster, 1 case meeting severe criteria per the FDA definition was observed in the placebo group. This case occurred 22 days post-Dose 3 (placebo) and met the severe criterion of 'clinical signs at rest indicative of severe systemic illness' (SpO_2 ≤93% on room air at sea level).

In the all-available efficacy (mITT) population, 2 cases meeting severe criteria per the FDA definition were observed, both in the placebo group. The two cases included the case in the evaluable efficacy population described above; an additional case occurred 31 days post-Dose 3 (placebo) and also met the severe criterion of 'clinical signs at rest indicative of severe systemic illness' (SpO_2 ≤93% on room air at

sea level). This second case occurred in a participant who was included in the evaluable efficacy population but was excluded from the evaluable analysis surveillance for COVID-19 disease after a disqualifying protocol violation (received prohibited medication [monoclonal antibodies]) before the date of his COVID-19 diagnosis.

Both severe cases (per FDA definition) occurred in participants who were baseline SARS-CoV-2 negative. Narratives were prepared for both severe cases.

No cases were reported that were based on CDC criteria for severe COVID-19.

3.3. Discussion

The ability to boost the vaccine-induced immune response was established in study C4591001, variation EMEA/H/C/005735/II/0067. It was shown that a booster dose results in antibody titres that are considerably higher than those observed after the 2nd dose. The SARS-CoV-2 neutralizing GMT ratio of 1 month after Dose 3 to 1 month after Dose 2 was 3.29 (2-sided 97.5% CI: 2.76, 3.91), which met the 1.5-fold noninferiority criterion (i.e., lower bound of the 2-sided 97.5% CI for GMR >0.67) and point estimate of GMR ≥0.8. The booster effects were mainly studied in adults 18 to 55 years of age. In this population, it has been shown that a third dose given approximately 6 months after the primary vaccination series more than restores neutralising titres, compared to what was seen one month after dose two. While the immunogenicity and reactogenicity of a third dose have been sufficiently characterised, the proper timing and impact of a third dose across different populations has not been established. The antibody titres in adolescents are generally higher than those observed in adults, which may lead to longer protection after the primary series in adolescents as compared to adults, albeit there are no data to underpin this.

Study C4591031 is the ongoing, randomized, placebo-controlled, Phase 3 booster efficacy study. Approximately 10,000 individuals ≥16 years of age were randomized 1:1 to receive a booster dose of BNT162b2 30 µg or placebo at least 6 months after completing the 2-dose primary series in Study C4591001 and followed up to at least 2 months (median 2.5) post-booster.

The study population had a median age of 53, the majority was overweight or obese and about half had relevant co-morbidities. The study cut-off date was 05.10.2021 and the efficacy follow-up about 2.5 months.

Randomization was stratified by age, such that approximately 60% of participants enrolled would be ≥16 to 55 years of age and approximately 40% of participants would be >55 years of age. This study was conducted mainly in the US. According to the MAH, the Delta variant was the most prevalent SARS-CoV-2 virus variant during the study period before first data cut-off at the main study country (USA) and also in South-Africa. At the same time, Gamma was the most prevalent virus variant in Brazil. Therefore, it can be concluded that the vaccine efficacy reported after the first interim analysis is mainly targeted against the Delta virus variant.

Sequencing of all, or a representative sample of, COVID-19 cases will be performed for the end of study analysis. However, it should be noted that following the first interim analysis result, participants were able to be unblinded and the original placebo recipients to receive BNT162b2. It is therefore likely that relatively few 2-dose participants will remain during the Omicron era.

The relative vaccine efficacy of a booster dose vs two primary doses in the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days post-booster was 95.3% (2-sided 95% CI: 89.5%, 98.3%), based on 6 cases in the BNT162b2 group and 123 cases in the placebo group. The relative VE was very similar in the evaluable efficacy population with or without evidence of SARS-CoV-2:

94.6% (2-sided 95% CI: 88.5%, 97.9%), based on 7 cases in the BNT162b2 group and 124 cases in the placebo group.

The RVE in the all-available efficacy (mITT) population from booster vaccination onwards was 89.8% (2-sided 95% CI: 82.6%, 94.4%), based on 15 cases in the BNT162b2 group and 141 cases in the placebo group reported after booster vaccination.

For all subgroups analysed including demographics, country, time interval between Dose 2 and the booster dose, and risk status, the confirmed COVID-19 cases were predominantly reported in the placebo group. The estimated RVE for most subgroups was >90%. Signs and symptoms associated with cases were fewer and milder in 3 dose arm compared to the 2 dose arm.

Emerging information about waning immunity resulted in the recommendations for booster dose in many countries, especially for people above 65 and with co-morbidities. The unblinding of the current study was therefore not preventable. For the next interim report, it might be made clear how many subjects accepted the booster dose in placebo arm.

It is noted that the inclusion criteria of the study had a lower age limit of 16 years of age. It is likely that protection following a booster dose is no less in the 16-17 year olds compared to older subjects. Immune responses are generally higher in younger subjects compared to older subjects. The relative efficacy not only takes the protection following the booster dose into account, but also the remaining efficacy of the two primary doses into account, i.e. assuming that protection wanes slower in younger subjects the relative efficacy of a third dose would be lower compared to that in older subjects.

In conclusion, Comirnaty has been shown to be at least as good at inducing neutralising antibody titers after the primary series in adolescents as in adults, and while the ability to boost the vaccine-induced immune response was only shown in adults, a booster response to the vaccine can equally be expected in adolescents.

4. Clinical Safety aspects

4.1. Methods – analysis of data submitted

This is a Phase 3 randomized, placebo-controlled, observer-blind substudy (C4591031) to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2 (30 µg). Participants ≥16 years of age from the pivotal Study C4591001 who completed a 2-dose primary series of BNT162b2 at least 6 months prior to randomization were enrolled, and participants were randomized at a ratio of 1:1 to receive either BNT162b2 or placebo.

Randomization was stratified by age, such that approximately 60% of participants enrolled would be ≥16 to 55 years of age and approximately 40% of participants >55 years of age. Participants randomized to receive placebo at the booster dose vaccination visit were offered the opportunity to receive BNT162b2 at a time decided by the sponsor agent.

On 22 September 2021, the FDA issued an EUA for a booster dose of BNT162b2 for select populations; therefore on 24 September 2021, the sponsor agent notified all study investigators that all C4591031 participants would now be eligible to be unblinded, and those participants who received placebo at the booster vaccination visit could choose to receive a booster dose of the vaccine as part of the study.

For all participants, information about AEs was collected for events occurring within approximately 1 month after vaccination, and information about SAEs was collected for events occurring approximately 6 months after each vaccination.

This study was conducted at 123 sites in Brazil (2), South Africa (4), and the US (117).

Key eligibility criteria for participants in this substudy are briefly summarized below:

- **Inclusion criteria:** healthy (pre-existing stable disease could include HIV, hepatitis C virus [HCV], or hepatitis B virus [HBV]); ≥16 years of age at Visit 1 (Day 1); had received 2 prior doses of 30µg BNT162b2 19-42 days apart, with the second dose in Study C4591001 being at least 175 days before Visit 1 (Day 1) in Study C4591031.
- **Exclusion criteria:** medical or psychiatric conditions, including previous diagnosis of COVID-19, that may have increased the risk of study participation or, in the investigator's judgment, made the participant inappropriate for the study (including immunocompromised individuals with known or suspected immunodeficiency); receipt of certain prior/concomitant therapies, which included radiotherapy, immunosuppressive therapy, prior COVID-19 vaccine other than BNT162b2, more than 2 prior doses of BNT162b2, or medication intended to treat COVID-19, as well as blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days prior to study administration, or antibody therapy specific to COVID-19, from 90 days prior to study intervention, or planned during the study.

Safety objective, endpoints and estimands are illustrated below:

Table 10. Objectives, Estimands and Endpoints

Objectives	Estimands	Endpoints
Primary Safety:	**Primary Safety:**	**Primary Safety:**
To define the safety profile of a booster dose of BNT162b2	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • AEs from the booster dose to 1 month after the booster dose[b] • SAEs from the booster dose to 6 months after the booster dose[a]	• AEs • SAEs

4.1.1. Disposition and Exposure

Table 11. Disposition of All Randomized Participants

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=5088) n[b] (%)	Placebo (N[a]=5048) n[b] (%)	Total (N[a]=10136) n[b] (%)
Randomized	5088 (100.0)	5048 (100.0)	10136 (100.0)
Not vaccinated with booster dose	6 (0.1)	5 (0.1)	11 (0.1)
Vaccinated with booster dose	5082 (99.9)	5043 (99.9)	10125 (99.9)
Blinded follow-up period			
Completed the 1-month telephone contact	5070 (99.6)	4973 (98.5)	10043 (99.1)
Withdrawn from the study	11 (0.2)	43 (0.9)	54 (0.5)
Withdrawn after booster vaccination and before the 1-month telephone contact	8 (0.2)	28 (0.6)	36 (0.4)
Withdrawn after the 1-month telephone contact	3 (0.1)	15 (0.3)	18 (0.2)
Reason for withdrawal from the study			
Withdrawal by participant	4 (0.1)	30 (0.6)	34 (0.3)
Lost to follow-up	6 (0.1)	10 (0.2)	16 (0.2)
Adverse event	0	1 (0.0)	1 (0.0)
Death	0	1 (0.0)	1 (0.0)
Protocol deviation	0	1 (0.0)	1 (0.0)
No longer meets eligibility criteria	1 (0.0)	0	1 (0.0)
Open-label period			
Unblinded before data cutoff	872 (17.1)	1185 (23.5)	2057 (20.3)
Unblinded after booster vaccination and before or on the same day of the 1-month telephone contact	3 (0.1)	40 (0.8)	43 (0.4)
Unblinded after the 1-month telephone contact	869 (17.1)	1145 (22.7)	2014 (19.9)

Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but not included in the analyses of the overall study objectives.
Note: Blinded follow-up period was censored to the cutoff date or the day before date of unblinding (per protocol) or the day before date of receiving COVID-19 vaccine off study, whichever date was earlier.
a. N = number of randomized participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adds Table Generation: 16OCT2021 (10:56)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adds_s002_all_rand

Unblinding to enter open-label follow-up (per protocol) occurred for 2057 participants (20.3%) prior to the data cut-off date (05 October 2021); 43 participants (0.4%) were unblinded after booster vaccination and prior to or on the same day of the 1-month telephone contact, and 2014 participants (19.9%) were unblinded after completing the 1-month post-booster telephone visit.

The most commonly reported type of important protocol deviation was related to meeting inclusion/exclusion criteria, which was balanced between the groups: 64 participants (1.3%) in the BNT162b2 booster group and 57 participants (1.1%) of the placebo booster group. This was predominately due to deviations from the requirement for receipt of the 2-dose series of BNT162b2 30 µg given 19-42 days apart, with the second dose being at least 175 days before booster study Visit 1 (Day 1). The next most common reported protocol deviation was related to receipt of other nonstudy COVID-19 vaccine at any time during the study, which was reported in 8 participants (0.2%) in the BNT162b2 group and 82 participants (1.6%) in the placebo group.

Table 12. Vaccine as Administered by Vaccine Group – Blinded Follow-up Period – All Randomized Participants

Vaccine (as Administered)	Vaccine Group (as Randomized)	
	BNT162b2 (30 µg) (N[a]=5088) n[b] (%)	Placebo (N[a]=5048) n[b] (%)
Vaccinated	5082 (99.9)	5043 (99.9)
Not vaccinated	6 (0.1)	5 (0.1)
Booster vaccination		
BNT162b2 (30 µg)	5081 (99.9)	0
Placebo	1 (0.0)	5043 (99.9)

Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adsl Table Generation: 15OCT2021 (14:43)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/advx_s002_adm_rand

Table 13. Vaccine Administration Timing – Blinded Follow-up Period – All Randomized Participants

	Vaccine Group (as Randomized)	
	BNT162b2 (30 µg) (N[a]=5088) n[b] (%)	Placebo (N[a]=5048) n[b] (%)
Randomized	5088 (100.0)	5048 (100.0)
Not vaccinated	6 (0.1)	5 (0.1)
Received booster vaccination	5082 (99.9)	5043 (99.9)
Time from Dose 2 of BNT162b2 (received in Study C4591001) to booster vaccination[c]		
<6 Months	14 (0.3)	6 (0.1)
≥6 Months to <8 months	752 (14.8)	732 (14.5)
≥8 Months to <10 months	819 (16.1)	833 (16.5)
≥10 Months to <12 months	3321 (65.3)	3298 (65.3)
≥12 Months	176 (3.5)	174 (3.4)
Mean (SD)	10.1 (1.62)	10.2 (1.59)
Median	10.8	10.7
Min, max	(5.0, 12.6)	(5.0, 12.8)

Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. First and second doses of BNT162b2 (30 µg) were received in Study C4591001.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adsl Table Generation: 16OCT2021 (02:37)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/advx_s002_time_rand_ia

As illustrated in the table below, the median duration of blinded follow-up after receipt of the booster vaccination for the safety population was 2.5 months as of the data cut-off date. Most participants (97.0%) had ≥2 to <4 months of follow-up after booster vaccination during the blinded follow-up period. The median duration of blinded follow-up time after booster vaccination was 2.5 months in the younger age group and 2.6 months in the older age group.

Table 14. Follow-up Time After Booster Vaccination – Blinded Follow-up Period – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=5081) n[b] (%)	Placebo (N[a]=5044) n[b] (%)	Total (N[a]=10125) n[b] (%)
Participants (%) with length of follow-up of:			
Blinded follow-up period			
<2 Months	99 (1.9)	204 (4.0)	303 (3.0)
≥2 Months to <4 months	4982 (98.1)	4840 (96.0)	9822 (97.0)
Mean (SD)	2.5 (0.29)	2.5 (0.35)	2.5 (0.32)
Median	2.5	2.5	2.5
Min, max	(0.4, 3.5)	(0.3, 3.5)	(0.3, 3.5)

Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but not included in the analyses of the overall study objectives.
Note: Follow-up time was calculated from booster vaccination to the cutoff date or withdrawal date or the day before date of unblinding (per protocol) or the day before date of receiving COVID-19 vaccine off study, whichever date was earlier.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adsl Table Generation: 16OCT2021 (02:37)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adsl_fu_d2_saf

4.1.2. Demographics

Table 15. Demographic Characteristics – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=5081) n[b] (%)	Placebo (N[a]=5044) n[b] (%)	Total (N[a]=10125) n[b] (%)
Sex			
Male	2457 (48.4)	2518 (49.9)	4975 (49.1)
Female	2624 (51.6)	2526 (50.1)	5150 (50.9)
Race			
White	3997 (78.7)	4002 (79.3)	7999 (79.0)
Black or African American	472 (9.3)	460 (9.1)	932 (9.2)
American Indian or Alaska Native	86 (1.7)	91 (1.8)	177 (1.7)
Asian	288 (5.7)	269 (5.3)	557 (5.5)
Native Hawaiian or other Pacific Islander	8 (0.2)	11 (0.2)	19 (0.2)
Multiracial	207 (4.1)	196 (3.9)	403 (4.0)
Not reported	23 (0.5)	15 (0.3)	38 (0.4)
Ethnicity			
Hispanic/Latino	760 (15.0)	748 (14.8)	1508 (14.9)
Non-Hispanic/non-Latino	4309 (84.8)	4288 (85.0)	8597 (84.9)
Not reported	12 (0.2)	8 (0.2)	20 (0.2)
Country			
Brazil	580 (11.4)	584 (11.6)	1164 (11.5)
South Africa	134 (2.6)	134 (2.7)	268 (2.6)
USA	4367 (85.9)	4326 (85.8)	8693 (85.9)
Age group (at vaccination)			
16-55 Years	2823 (55.6)	2797 (55.5)	5620 (55.5)
>55 Years	2258 (44.4)	2247 (44.5)	4505 (44.5)
16-17 Years	46 (0.9)	44 (0.9)	90 (0.9)
18-55 Years	2777 (54.7)	2753 (54.6)	5530 (54.6)
56-64 Years	1083 (21.3)	1059 (21.0)	2142 (21.2)
65+ Years	1175 (23.1)	1188 (23.6)	2363 (23.3)
Age at vaccination (years)			
Mean (SD)	51.8 (15.24)	51.7 (15.33)	51.7 (15.28)
Median	53.0	53.0	53.0
Min, max	(16, 86)	(16, 87)	(16, 87)
Baseline SARS-CoV-2 status			
Positive[c]	284 (5.6)	261 (5.2)	545 (5.4)
Negative[d]	4789 (94.3)	4775 (94.7)	9564 (94.5)
Unknown	8 (0.2)	8 (0.2)	16 (0.2)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	57 (1.1)	49 (1.0)	106 (1.0)
Normal weight (≥18.5-24.9 kg/m^2)	1431 (28.2)	1459 (28.9)	2890 (28.5)
Overweight (≥25.0-29.9 kg/m^2)	1768 (34.8)	1725 (34.2)	3493 (34.5)
Obese (≥30.0 kg/m^2)	1823 (35.9)	1811 (35.9)	3634 (35.9)
Missing	2 (0.0)	0	2 (0.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
d. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adsl Table Generation: 15OCT2021 (14:43)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adsl_s005_demo_ia

The safety population included a total of 10,125 participants: 5081 in the BNT162b2 group and 5044 in the placebo group. Of the 11 (0.1%) participants total excluded from the safety population, all were

excluded because they did not receive study intervention. A total of 50 (0.5%) participants in the safety population had confirmed stable HIV disease, including 26 in the BNT162b2 group and 24 in the placebo group. HIV+ participants were included in this safety population summary and were analysed separately for safety endpoint analyses.

Baseline Charlson comorbidities were reported by 2390 participants (23.6%) in the safety population and were balanced across the BNT162b2 and placebo groups. The most common comorbidities reported overall were chronic pulmonary disease in 927 participants (9.2%), diabetes without chronic complication in 845 participants (8.3%), and any malignancy in 469 participants (4.6%).

Participants in the safety population had a diverse medical history profile that is consistent with that of prior analyses of Phase 2/3 C4591001 participants. Medical history SOCs were balanced across the BNT162b2 and placebo groups. In the BNT162b2 recipients, conditions in the surgical and medical procedures (48.2%), metabolism and nutrition disorders (35.8%), and immune system disorders (35.7%, including seasonal allergy in 20.3%) SOCs were most frequently reported.

The younger age group (16 to 55 years of age) made up 55.5% of the safety population; this included 90 participants (0.9%) who were 16 to 17 years of age. The older age group (>55 years of age) made up 44.5% of the safety population; this included 2363 participants (23.3%) who were ≥65 years of age. Demographics (except for age) in the younger and older age groups were similar to the overall safety population. The median age in the younger group was 42.0 years, and the median age in the older group was 65.0 years.

Baseline Charlson comorbidities were reported at higher frequencies in the older group (33.2%) than in the younger group (15.9%). The most commonly reported comorbidities in both age groups were the same as reported in the safety population overall, albeit reported at higher frequencies in the older group compared to the younger group.

4.2. Results

4.2.1. Local Reactions and Systemic Events

The C4591031 safety endpoints for Substudy A did not include solicited reactogenicity (local reactions, systemic events) of BNT162b2 captured via e-diary. In Study C4591001, reactogenicity of BNT162b2 was typically mild to moderate and short-lived; further details for participants at least 16 years of age, as in this study, are provided in the C4591001 final analysis (03 December 2020), 6-month update (29 April 2021), and booster (Dose 3) (23 August 2021) interim CSRs.

4.2.2. Adverse Events

An overview of AEs from administration of booster vaccination to the data cut-off date (05 October 2021), which represents up to at least 2 months post-booster follow-up is shown in the table below. As there was no use of an electronic diary to record local reactions or systemic events, all such events were reported as AEs.

From booster vaccination to the data cut-off date, a greater proportion of participants in the BNT162b2 (25.2%) reported any AE compared with the placebo group (6.8%). This was driven primarily by any AEs considered by the investigator as related to study intervention, reported by 23.4% participants in the BNT162b2 group and 4.2% participants in the placebo group. Any severe or serious AEs were reported across the BNT162b2 and placebo groups by ≤0.8% and ≤0.5%, respectively.

Table 16. Number (%) of Participants Reporting at Least 1 Adverse Event From Booster Vaccination to Cut-off Date – Blinded Follow-up Period – Safety Population

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 (30 µg) (N[a]=5055) n[b] (%)	Placebo (N[a]=5020) n[b] (%)
Any adverse event	1275 (25.2)	339 (6.8)
Related[c]	1182 (23.4)	209 (4.2)
Severe	38 (0.8)	22 (0.4)
Life-threatening	1 (0.0)	4 (0.1)
Any serious adverse event	16 (0.3)	24 (0.5)
Related[c]	3 (0.1)	2 (0.0)
Severe	10 (0.2)	18 (0.4)
Life-threatening	1 (0.0)	4 (0.1)
Any nonserious adverse event	1266 (25.0)	325 (6.5)
Related[c]	1180 (23.3)	209 (4.2)
Severe	31 (0.6)	5 (0.1)
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 participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any event," n = number of participants reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adae Table Generation: 15OCT2021 (14:47)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adae_s091_cut_saf

According to the MAH few additional AEs were reported between 1 month after booster vaccination to the data cut-off date. One participant in the placebo group (in the older >55 years of age group) had life-threatening SAEs leading to withdrawal, and one other participant in the placebo group died due to an unrelated SAE.

4.2.2.1. Adverse Events by SOCs and PTs

From booster vaccination to the data cut-off date, any AEs were reported at a higher frequency in the BNT162b2 group (25.2%) than the placebo group (6.8%) (Table 16). Most AEs reported during this period reflect reactogenicity events. AE frequencies in SOCs for reactogenicity terms in the BNT162b2 versus placebo groups were:

- general disorders and administration site conditions: 21.0% vs 3.1%
- musculoskeletal and connective tissue disorders: 6.7% vs 0.9%
- nervous system disorders: 5.6% vs 1.3%
- gastrointestinal disorders: 1.7% vs 0.8%.

Overall, most AEs observed during the reporting period up to the data cut-off date were largely attributable to reactogenicity and similar terms (i.e., nausea, malaise, body temperature increased), or to lymphadenopathy (reported in 135 [2.7%] in the BNT162b2 group and 2 [0.0%] in the placebo group). This is consistent with the AE profile previously observed following Dose 2 of the initial 2-dose regimen.

The AE profiles from booster vaccination to the data cut-off date in the younger (16 to 55 years of age) and older (>55 years of age) age groups were similar to the overall safety population.

Table 17. Number (%) of Participants Reporting at Least 1 Adverse Event From Booster Vaccination to Cut-off Date, by System Organ Class and Preferred Term – Blinded Follow-up Period – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N=5055)		Placebo (N=5020)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	1275 (25.2)	(24.0, 26.4)	339 (6.8)	(6.1, 7.5)
Blood and lymphatic system disorders	140 (2.8)	(2.3, 3.3)	2 (0.0)	(0.0, 0.1)
Lymphadenopathy	135 (2.7)	(2.2, 3.2)	2 (0.0)	(0.0, 0.1)
Lymph node pain	4 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Lymphadenitis	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Iron deficiency anaemia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Lymphopenia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Neutropenia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Thrombocytopenia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Cardiac disorders	9 (0.2)	(0.1, 0.3)	5 (0.1)	(0.0, 0.2)
Palpitations	4 (0.1)	(0.0, 0.2)	1 (0.0)	(0.0, 0.1)
Tachycardia	3 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Acute myocardial infarction	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Coronary artery insufficiency	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Myocardial infarction	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Supraventricular tachycardia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Ventricular extrasystoles	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Ear and labyrinth disorders	3 (0.1)	(0.0, 0.2)	1 (0.0)	(0.0, 0.1)
Vertigo	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Ear pain	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Vertigo positional	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Endocrine disorders	1 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Hypothyroidism	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Thyroid cyst	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Eye disorders	8 (0.2)	(0.1, 0.3)	2 (0.0)	(0.0, 0.1)
Glaucoma	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Photophobia	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Chalazion	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Diplopia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Dry eye	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Eye pain	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Eyelid ptosis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Keratitis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Vitreous detachment	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Gastrointestinal disorders	85 (1.7)	(1.3, 2.1)	42 (0.8)	(0.6, 1.1)
Nausea	48 (0.9)	(0.7, 1.3)	16 (0.3)	(0.2, 0.5)

Diarrhoea	25 (0.5)	(0.3, 0.7)	13 (0.3)	(0.1, 0.4)
Vomiting	11 (0.2)	(0.1, 0.4)	2 (0.0)	(0.0, 0.1)
Gastrooesophageal reflux disease	2 (0.0)	(0.0, 0.1)	5 (0.1)	(0.0, 0.2)
Abdominal pain upper	2 (0.0)	(0.0, 0.1)	4 (0.1)	(0.0, 0.2)
Abdominal pain	2 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Dyspepsia	3 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Toothache	0	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Abdominal discomfort	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Aphthous ulcer	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Constipation	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Dental caries	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Dental cyst	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Diverticulum	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Dry mouth	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Gingival pain	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Haemorrhoids	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Hypoaesthesia oral	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Hypoaesthesia teeth	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Inguinal hernia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Intestinal obstruction	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Paraesthesia oral	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Parotid duct obstruction	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
General disorders and administration site conditions	1063 (21.0)	(19.9, 22.2)	156 (3.1)	(2.6, 3.6)
Injection site pain	651 (12.9)	(12.0, 13.8)	78 (1.6)	(1.2, 1.9)
Fatigue	366 (7.2)	(6.5, 8.0)	63 (1.3)	(1.0, 1.6)
Pyrexia	242 (4.8)	(4.2, 5.4)	7 (0.1)	(0.1, 0.3)
Chills	233 (4.6)	(4.0, 5.2)	9 (0.2)	(0.1, 0.3)
Pain	135 (2.7)	(2.2, 3.2)	15 (0.3)	(0.2, 0.5)
Malaise	35 (0.7)	(0.5, 1.0)	4 (0.1)	(0.0, 0.2)
Injection site erythema	22 (0.4)	(0.3, 0.7)	0	(0.0, 0.1)
Injection site swelling	21 (0.4)	(0.3, 0.6)	1 (0.0)	(0.0, 0.1)
Axillary pain	13 (0.3)	(0.1, 0.4)	1 (0.0)	(0.0, 0.1)
Asthenia	8 (0.2)	(0.1, 0.3)	1 (0.0)	(0.0, 0.1)
Injection site bruising	3 (0.1)	(0.0, 0.2)	3 (0.1)	(0.0, 0.2)
Chest pain	2 (0.0)	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)
Injection site reaction	5 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Feeling hot	4 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Injection site pruritus	4 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Swelling	4 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Injection site inflammation	3 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Injection site oedema	3 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Peripheral swelling	2 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Feeling abnormal	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Injection site induration	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Vaccination site pain	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Chest discomfort	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Cyst	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Drug withdrawal syndrome	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Injection site discomfort	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Injection site hypoaesthesia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Injection site irritation	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Injection site paraesthesia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Injection site rash	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Injection site vesicles	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Injection site warmth	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Injury associated with device	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Vaccination site rash	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Hepatobiliary disorders	2 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Cholelithiasis	2 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Hepatic steatosis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Immune system disorders	0	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)
Allergic oedema	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Allergy to arthropod sting	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Seasonal allergy	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Infections and infestations	27 (0.5)	(0.4, 0.8)	32 (0.6)	(0.4, 0.9)
Urinary tract infection	3 (0.1)	(0.0, 0.2)	9 (0.2)	(0.1, 0.3)
Cellulitis	3 (0.1)	(0.0, 0.2)	1 (0.0)	(0.0, 0.1)
Acute sinusitis	2 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Cystitis	1 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Ear infection	2 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Herpes zoster	2 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Appendicitis perforated	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Candida infection	0	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Diverticulitis	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Otitis externa	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Abscess	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Adenoiditis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)

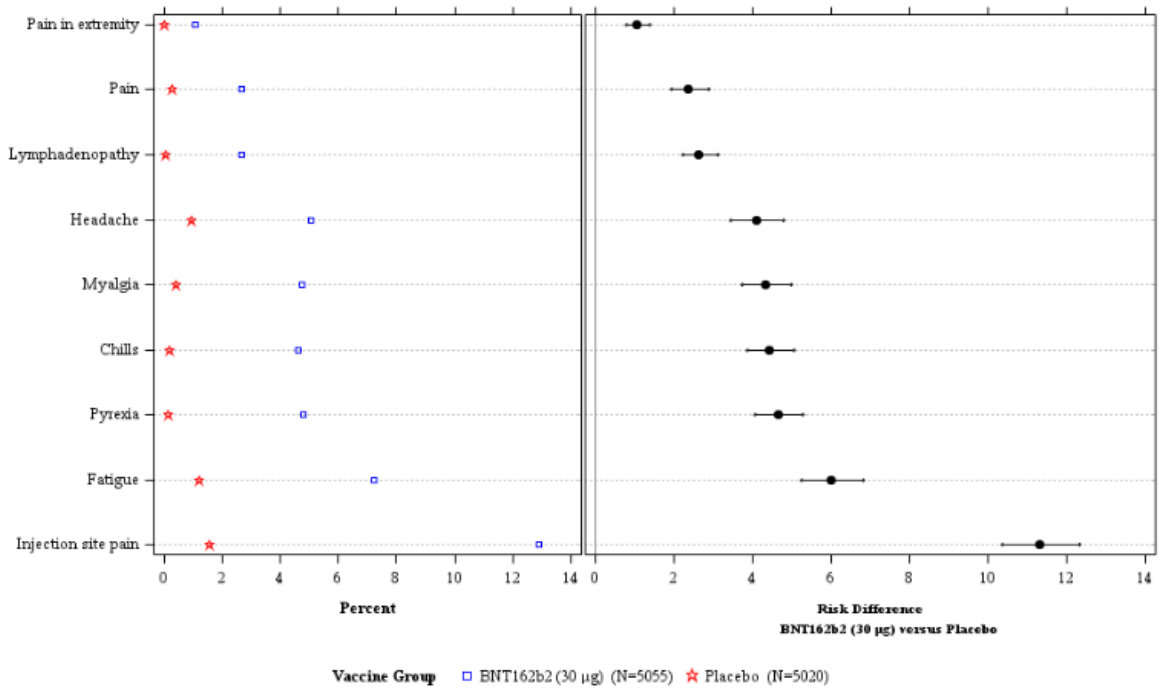
Appendicitis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Arthritis infective	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
COVID-19 pneumonia	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Conjunctivitis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Epididymitis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Eye infection	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Groin abscess	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Hand-foot-and-mouth disease	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Helicobacter infection	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Hordeolum	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Infected dermal cyst	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Kidney infection	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Latent tuberculosis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Mastitis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Onychomycosis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Oral herpes	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Otitis media	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Otitis media acute	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Peritonitis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Pneumonia	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Salmonellosis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Sepsis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Sinusitis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Tooth abscess	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Vestibular neuronitis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Vulvovaginal mycotic infection	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Injury, poisoning and procedural complications	15 (0.3)	(0.2, 0.5)	26 (0.5)	(0.3, 0.8)
Fall	3 (0.1)	(0.0, 0.2)	2 (0.0)	(0.0, 0.1)
Ligament sprain	1 (0.0)	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)
Muscle strain	1 (0.0)	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)
Skin laceration	3 (0.1)	(0.0, 0.2)	1 (0.0)	(0.0, 0.1)
Arthropod sting	1 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Contusion	0	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Joint injury	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Procedural pain	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Acetabulum fracture	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Animal bite	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Ankle fracture	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Arthropod bite	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Bone contusion	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Corneal abrasion	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Craniocerebral injury	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Exposure during pregnancy	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Head injury	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Hip fracture	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Humerus fracture	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Limb crushing injury	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Limb injury	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Musculoskeletal injury	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Neck injury	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Pelvic fracture	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Periorbital haemorrhage	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Post procedural haemorrhage	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Road traffic accident	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Skin abrasion	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Stress fracture	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Tendon rupture	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Thoracic vertebral fracture	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Investigations	34 (0.7)	(0.5, 0.9)	11 (0.2)	(0.1, 0.4)
Body temperature increased	30 (0.6)	(0.4, 0.8)	3 (0.1)	(0.0, 0.2)
Hepatic enzyme increased	2 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Prostatic specific antigen increased	0	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Antinuclear antibody positive	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Blood creatinine increased	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Blood glucose increased	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Blood pressure increased	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Heart rate increased	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Lipase increased	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Respiratory rate increased	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Metabolism and nutrition disorders	16 (0.3)	(0.2, 0.5)	11 (0.2)	(0.1, 0.4)
Decreased appetite	9 (0.2)	(0.1, 0.3)	0	(0.0, 0.1)
Gout	0	(0.0, 0.1)	4 (0.1)	(0.0, 0.2)
Type 2 diabetes mellitus	2 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Dehydration	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Hypercholesterolaemia	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Hypokalaemia	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Vitamin D deficiency	0	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)

Diabetes mellitus	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Diabetic ketoacidosis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Hyponatraemia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Musculoskeletal and connective tissue disorders	341 (6.7)	(6.1, 7.5)	43 (0.9)	(0.6, 1.2)
Myalgia	239 (4.7)	(4.2, 5.3)	20 (0.4)	(0.2, 0.6)
Arthralgia	42 (0.8)	(0.6, 1.1)	13 (0.3)	(0.1, 0.4)
Pain in extremity	54 (1.1)	(0.8, 1.4)	1 (0.0)	(0.0, 0.1)
Neck pain	9 (0.2)	(0.1, 0.3)	2 (0.0)	(0.0, 0.1)
Back pain	7 (0.1)	(0.1, 0.3)	2 (0.0)	(0.0, 0.1)
Synovial cyst	4 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Muscular weakness	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Musculoskeletal chest pain	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Musculoskeletal stiffness	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Tendonitis	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Bone cyst	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Bone pain	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Groin pain	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Intervertebral disc protrusion	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Joint effusion	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Joint stiffness	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Joint swelling	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Muscle fatigue	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Muscle swelling	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Musculoskeletal discomfort	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Musculoskeletal pain	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Osteoarthritis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Pain in jaw	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Plantar fasciitis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Psoriatic arthropathy	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Rotator cuff syndrome	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Scoliosis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Trigger finger	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (0.1)	(0.1, 0.3)	9 (0.2)	(0.1, 0.3)
Basal cell carcinoma	2 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Benign neoplasm of thyroid gland	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Breast cancer	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Focal nodular hyperplasia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Follicular lymphoma	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Lung carcinoma cell type unspecified stage II	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Malignant melanoma	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Melanocytic naevus	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Metastases to diaphragm	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Metastases to liver	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Pancreatic carcinoma	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Pancreatic carcinoma metastatic	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Prostate cancer	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Renal cancer metastatic	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Renal cell carcinoma	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Squamous cell carcinoma of skin	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Nervous system disorders	285 (5.6)	(5.0, 6.3)	63 (1.3)	(1.0, 1.6)
Headache	255 (5.0)	(4.5, 5.7)	49 (1.0)	(0.7, 1.3)
Lethargy	12 (0.2)	(0.1, 0.4)	3 (0.1)	(0.0, 0.2)
Dizziness	9 (0.2)	(0.1, 0.3)	3 (0.1)	(0.0, 0.2)
Migraine	2 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Paraesthesia	2 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Syncope	3 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Cerebrovascular accident	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Dysgeusia	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Hyperaesthesia	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Hypoaesthesia	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Altered state of consciousness	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Bell's palsy	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Cerebral venous thrombosis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Cervical radiculopathy	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Cervicobrachial syndrome	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Hypotonia	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Parosmia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Sciatica	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Seizure	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Somnolence	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Taste disorder	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Tension headache	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Toxic encephalopathy	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Tremor	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Pregnancy, puerperium and perinatal conditions	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Abortion spontaneous	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)

Psychiatric disorders	11 (0.2)	(0.1, 0.4)	10 (0.2)	(0.1, 0.4)
Anxiety	3 (0.1)	(0.0, 0.2)	2 (0.0)	(0.0, 0.1)
Attention deficit hyperactivity disorder	0	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)
Insomnia	2 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Adjustment disorder with mixed anxiety and depressed mood	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Stress	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Abnormal dreams	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Alcoholism	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Depression	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Generalised anxiety disorder	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Mood altered	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Nightmare	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Poor quality sleep	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Suicidal ideation	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Renal and urinary disorders	8 (0.2)	(0.1, 0.3)	1 (0.0)	(0.0, 0.1)
Haematuria	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Nephrolithiasis	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Dysuria	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Renal colic	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Renal cyst	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Stress urinary incontinence	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Urinary incontinence	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Reproductive system and breast disorders	6 (0.1)	(0.0, 0.3)	4 (0.1)	(0.0, 0.2)
Prostatitis	0	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Adenomyosis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Atrophic vulvovaginitis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Breast calcifications	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Breast pain	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Heavy menstrual bleeding	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Intermenstrual bleeding	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Ovarian cyst	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Scrotal disorder	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Respiratory, thoracic and mediastinal disorders	12 (0.2)	(0.1, 0.4)	13 (0.3)	(0.1, 0.4)
Asthma	2 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Nasal congestion	3 (0.1)	(0.0, 0.2)	1 (0.0)	(0.0, 0.1)
Rhinorrhoea	3 (0.1)	(0.0, 0.2)	1 (0.0)	(0.0, 0.1)
Pulmonary embolism	0	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)
Sinus congestion	2 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Epistaxis	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Sneezing	0	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Asthma exercise induced	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Chronic obstructive pulmonary disease	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Dyspnoea	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Nasal polyps	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Pharyngeal swelling	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Pulmonary congestion	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Respiratory failure	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Throat tightness	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Skin and subcutaneous tissue disorders	23 (0.5)	(0.3, 0.7)	10 (0.2)	(0.1, 0.4)
Hyperhidrosis	4 (0.1)	(0.0, 0.2)	1 (0.0)	(0.0, 0.1)
Night sweats	5 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Pruritus	3 (0.1)	(0.0, 0.2)	2 (0.0)	(0.0, 0.1)
Rash	4 (0.1)	(0.0, 0.2)	1 (0.0)	(0.0, 0.1)
Dermatitis contact	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Urticaria	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Alopecia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Alopecia areata	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Cold sweat	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Dermal cyst	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Dermatitis allergic	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Dry skin	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Erythema	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Intertrigo	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Psoriasis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Rash erythematous	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Rash papular	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Surgical and medical procedures	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Bunion operation	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Vascular disorders	6 (0.1)	(0.0, 0.3)	9 (0.2)	(0.1, 0.3)
Hypertension	3 (0.1)	(0.0, 0.2)	2 (0.0)	(0.0, 0.1)
Hot flush	2 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Flushing	0	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)
Deep vein thrombosis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Haematoma	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Hypotension	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Peripheral venous disease	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adae Table Generation: 15OCT2021 (14:47)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adae_s130_cut_saf

Figure 2. Forest Plot of Adverse Events Reported in ≥1% of Participants in Either Vaccine Group from Booster Vaccination to 1 Month After Booster Vaccination – Blinded Follow-Up Period – Safety Population



Note: MedDRA (v24.0) coding dictionary applied.
Note: A MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants with the AE term in at least 1 vaccine group.
Note: 2-Sided CI based on the Miettinen and Numminen method for the differences in proportions (BNT162b2 [30 µg] - placebo) expressed as a percentage. They are not adjusted for multiplicity and should be used for screening purposes only.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adae Table Generation: 25OCT2021 (16:03)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: /nda2_ubBIA/C4591031_A_IA_1/adae_f001_t2

Severe or Life-Threatening Adverse Events

The frequencies of severe or life-threatening events after the booster dose were low (≤0.7%) across the BNT162b2 and placebo groups.

From booster vaccination to 1 month after booster vaccination, severe events were reported by 33 participants (0.7%) in the BNT162b2 group and 16 participants (0.3%) in the placebo group. The higher frequency of severe events in the BNT162b2 group was mostly due to severe reactogenicity events (ie, fatigue, pyrexia, injection site pain, myalgia, and headache). Life-threatening (or Grade 4) events were reported by 1 participant in the BNT162b2 group (acute myocardial infarction) and 2 participants in the placebo group (n=1 each with acute myocardial infarction and pancreatic carcinoma). These were reported as SAEs.

4.2.2.2. Adverse Events of Special Interest

Table 18. Number (%) of Participants Reporting at Least 1 Adverse Event of Special Interest From Booster Vaccination to Cut-off Date, by System Organ Class and Preferred Term – Blinded Follow-up Period – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=5055) n[b] (%)	(95% CI[c])	Placebo (N[a]=5020) n[b] (%)	(95% CI[c])	Difference %[d]	(95% CI[e])
Blood and lymphatic system disorders						
Lymphopenia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Neutropenia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Thrombocytopenia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Cardiac disorders						
Tachycardia	3 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)	0.1	(-0.0, 0.2)
Acute myocardial infarction	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Myocardial infarction	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Endocrine disorders						
Hypothyroidism	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
General disorders and administration site conditions						
Pyrexia	242 (4.8)	(4.2, 5.4)	7 (0.1)	(0.1, 0.3)	4.6	(4.1, 5.3)
Swelling	4 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)	0.1	(0.0, 0.2)
Injection site bruising	3 (0.1)	(0.0, 0.2)	3 (0.1)	(0.0, 0.2)	-0.0	(-0.1, 0.1)
Chest pain	2 (0.0)	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)	-0.0	(-0.1, 0.1)
Chest discomfort	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Immune system disorders						
Allergic oedema	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Infections and infestations						
Herpes zoster	2 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	0.0	(-0.1, 0.1)
Oral herpes	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
COVID-19 pneumonia	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Pneumonia	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Injury, poisoning and procedural complications						
Bone contusion	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Periorbital haemorrhage	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Post procedural haemorrhage	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Contusion	0	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.0)
Investigations						
Hepatic enzyme increased	2 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Antinuclear antibody positive	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Metabolism and nutrition disorders						
Diabetes mellitus	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Diabetic ketoacidosis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Musculoskeletal and connective tissue disorders						
Arthralgia	42 (0.8)	(0.6, 1.1)	13 (0.3)	(0.1, 0.4)	0.6	(0.3, 0.9)
Psoriatic arthropathy	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Nervous system disorders						

Cerebrovascular accident	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Seizure	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Bell's palsy	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Cerebral venous thrombosis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Renal and urinary disorders						
Haematuria	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Reproductive system and breast disorders						
Heavy menstrual bleeding	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Intermenstrual bleeding	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Respiratory, thoracic and mediastinal disorders						
Asthma	2 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Epistaxis	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.0, 0.1)
Pharyngeal swelling	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Throat tightness	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Dyspnoea	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Pulmonary embolism	0	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)	-0.1	(-0.2, 0.0)
Respiratory failure	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Sneezing	0	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.0)
Skin and subcutaneous tissue disorders						
Rash	4 (0.1)	(0.0, 0.2)	1 (0.0)	(0.0, 0.1)	0.1	(-0.0, 0.2)
Pruritus	3 (0.1)	(0.0, 0.2)	2 (0.0)	(0.0, 0.1)	0.0	(-0.1, 0.1)
Urticaria	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.0, 0.1)
Alopecia areata	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Erythema	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Psoriasis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Rash erythematous	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Vascular disorders						
Haematoma	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)	0.0	(-0.1, 0.1)
Deep vein thrombosis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)
Flushing	0	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)	-0.1	(-0.2, 0.0)
Hypotension	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)	-0.0	(-0.1, 0.1)

Note: MedDRA (v24.0) coding dictionary applied.
Note: The 95% confidence interval quantifies the precision of the incidence rate difference estimate. Confidence intervals are not adjusted for multiplicity. They should only be used to identify potentially important adverse events.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (BNT162b2 [30 µg] - placebo).
e. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adae Table Generation: 15OCT2021 (14:47)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adae_aesi_soc_saf

Lymphadenopathy

Lymphadenopathy is considered an adverse reaction to the vaccine. A total of 135 participants (2.7%) in the BNT162b2 group and 2 (0.0%) in the placebo group had cases of lymphadenopathy reported post-booster. Most cases in the BNT162b2 group (134 [2.7%]) and 1 case (1 [0.0%]) in the placebo group were considered by the investigator as related to study intervention. Cases of lymphadenopathy typically were mild to moderate, occurred within 1 to 3 days after BNT162b2 booster dose administration, located in the axilla or cervical nodes, and recovered/resolved (most within 1 to 3 days after onset). Lymphadenopathy frequency among BNT162b2 recipients was higher in younger (18 to 55 years of age) compared with older (>55 years of age) participants (4.2% vs 1.0%), and higher in female participants than in male participants (3.5% vs 1.8%). Other events similar to lymphadenopathy reported in the BNT162b2 group were axillary pain, lymph node pain, and lymphadenitis reported by 13 participants (0.3%), 4 participants (0.1%), and 2 participants (0.0%), respectively.

Appendicitis

Appendicitis/perforated appendicitis was reported by 2 participants (0.1%) in the BNT162b2 group and none in the placebo group (these events were SAEs). These SAEs occurred post-booster with onset of 50

days (2 events of appendicitis and perforated appendicitis both reported in same participant) or 70 days (perforated appendicitis) and were all considered to be not related to study intervention.

Bell's Palsy

Bell's palsy was reported by 1 participant in the placebo group. This participant, 25-34 years of age, had reported moderate right-side Bell's palsy with onset at 15 days after Dose 3 (placebo), reported as recovering/resolving at the time of the data cut-off date. He had received his second dose of the BNT162b2 primary 2-dose series and a booster dose of placebo 296 days later. This case was considered as not related to study intervention.

Other AESI

Additional AEs of clinical interest, including those on the CDC AESI list, were evaluated based on sponsor safety data review. These AEs were identified from the C4591031 study database as of the data cut-off date (05 October 2021). From this analysis, notable pertinent negatives (ie, no cases reported in this population as of the data cut-off for this submission) with regard to the CDC list of AESIs included (but were not limited to): thromboembolic or intravascular coagulation events, autoimmune or demyelination events, meningitis, encephalitis, optic neuritis, Kawasaki disease, MIS-C, or acute respiratory distress syndrome.

Blood and Lymphatic Disorders

There was no imbalance between BNT162b2 and placebo groups, based on risk difference in the blood and lymphatic system disorders SOC; however, there was 1 participant in the BNT162b2 group who had concurrent non-serious events of mild transient lymphopenia and thrombocytopenia, and severe neutropenia:

A participant **45-54 years** of age had concurrent events of **mild transient lymphopenia and thrombocytopenia, and severe neutropenia**, all with an onset of 4 days post-booster and all considered by the investigator as related to study intervention. On Study Day 2, the participant presented with mild to moderate AEs including injection site pain, chills, prostration, and headache which all ended on Study Day 3, and left axillary lymphadenopathy which ended on Study Day 4. According to the investigator, the participant took metamizole (1 g every 4 hours, Study Days 2-3) as a treatment for headache and pain at the injection site. According to the investigator, laboratory testing was conducted since the participant was not feeling well post-investigational product administration. The lymphopenia and thrombocytopenia were reported as recovered/resolved 4 days after onset. The neutropenia was reported as resolved 62 days after onset. The participant did not have any concurrent medical conditions of concern; however, the participant was taking metamizole for the treatment of her reactogenicity. This NSAID, has been withdrawn from several international markets, including the US in 1979 due to cases of fatal agranulocytosis. In a recent study of metamizole-associated neutropenia in 48 patients treated in Switzerland between 2005 and 2017, of whom 40% received metamizole for <7 days when diagnosed with neutropenia, over two-thirds had agranulocytosis (neutrophil drop to <0.5 x 109 cell/L), and nearly 30% had values between 0.5-1.0 x 109/L.10 The white blood cell (WBC) count may respond as early as 48 hours after cessation of metamizole, but more commonly normalizes within 1 week and can take up to 1 month. The investigator noted in a personal communication with the Sponsor that the use of this medication 'may be a plausible cause for this finding.

Table 19. Laboratory Values for Participant with Abnormal White Blood Cell Counts

Date (Day)	WBC[b,c]	Neutrophils	Lymphocytes	Eosinophils[b]	Platelets[c]
05 Jan 2021 (Prior to study entry)	5,010	2,440/mm³ (NR: 1700 - 8000/mm³)	2,099/mm³ (NR: 900 - 2900/mm³)	50	189,000 (150,000 - 450,000)
31 Jul 2021 (Day 4)	1,550	481 and 559/mm³ (NR: 1600 - 7700/mm³)[a]	822/mm³ (NR: 1000 - 3900/mm³)	78	126,000 (140,000 - 500,000)
03 Aug 2021 (Day 7)	3,520	1,271/mm³ (NR: 1580 - 7700/mm³)	1,728/mm³ (NR: 740 - 5500/mm³)	109	164,000 (130,000 - 450,000)
12 Aug 2021 (Day 16)	3,710	1,551[b]	1,781[b]	82	232,000[b]

NR = normal range; WBC = white blood cells. [a]Two values obtained, [b]Normal ranges not provided by the site, [c] Units not provided.

Cardiac Disorders

There was a numerical difference for events of **tachycardia**, which was reported by **3 participants** (0.1%) in the **BNT162b2 group** compared with none in the placebo group. Two of these events were reported at 1 day or 8 days post-booster, respectively, and the third event was reported at 31 days post-booster. One of the events was an SAE. Three cases (n=1 in BNT162b2 and n=2 in placebo, 0.0% each) were reported of myocardial infarction or acute myocardial infarction, showing no imbalance between groups; all of these events were unrelated except 1 event of acute myocardial infarction in the placebo group considered by the investigator as related to study intervention.

Nervous System Disorders

There was no imbalance between BNT162b2 and placebo groups based on risk difference in the nervous system disorders SOC; however, 1 event of clinical interest of cerebral venous thrombosis was noted in a 35-44 year old participant who received a booster dose of placebo.

4.2.2.3. Serious Adverse Events and Death

Death

As of the data cut-off date (05 October 2021), 1 participant in the placebo group died due to an unrelated SAE of pulmonary embolism. This participant 55-64 years of age died from pulmonary embolism which occurred 52 days after receipt of booster vaccination (placebo).

Serious Adverse Events (SAEs)

From booster vaccination to the data cut-off date, SAEs were reported in 16 participants (0.3%) in the BNT162b2 group and 24 participants (0.5%) in the placebo group. Most of these SAEs were considered as not related to study intervention.

Table 20. Number (%) of Participants Reporting at Least 1 Serious Adverse Event From Booster Vaccination to Cut-off Date, by System Organ Class and Preferred Term – Blinded Follow-up Period – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=5055)		Placebo (N[a]=5020)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	16 (0.3)	(0.2, 0.5)	24 (0.5)	(0.3, 0.7)

Cardiac disorders	2 (0.0)	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)
Acute myocardial infarction	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Myocardial infarction	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Tachycardia	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Ventricular extrasystoles	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Gastrointestinal disorders	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Intestinal obstruction	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
General disorders and administration site conditions	0	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Chest pain	0	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Infections and infestations	4 (0.1)	(0.0, 0.2)	4 (0.1)	(0.0, 0.2)
Appendicitis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Appendicitis perforated	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
COVID-19 pneumonia	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Diverticulitis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Pneumonia	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Salmonellosis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Sepsis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Urinary tract infection	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Injury, poisoning and procedural complications	1 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.1)
Acetabulum fracture	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Hip fracture	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Pelvic fracture	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Thoracic vertebral fracture	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Investigations	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Hepatic enzyme increased	2 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Musculoskeletal and connective tissue disorders	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Intervertebral disc protrusion	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Osteoarthritis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.0)	(0.0, 0.1)	5 (0.1)	(0.0, 0.2)
Follicular lymphoma	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Lung carcinoma cell type unspecified stage II	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Metastases to diaphragm	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Metastases to liver	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Pancreatic carcinoma	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Pancreatic carcinoma metastatic	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Prostate cancer	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Renal cancer metastatic	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Renal cell carcinoma	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Nervous system disorders	3 (0.1)	(0.0, 0.2)	2 (0.0)	(0.0, 0.1)
Cerebrovascular accident	1 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Cerebral venous thrombosis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Syncope	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Toxic encephalopathy	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Pregnancy, puerperium and perinatal conditions	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Abortion spontaneous	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Psychiatric disorders	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Suicidal ideation	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Renal and urinary disorders	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Nephrolithiasis	1 (0.0)	(0.0, 0.1)	0	(0.0, 0.1)
Reproductive system and breast disorders	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Adenomyosis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Respiratory, thoracic and mediastinal disorders	0	(0.0, 0.1)	6 (0.1)	(0.0, 0.3)
Pulmonary embolism	0	(0.0, 0.1)	3 (0.1)	(0.0, 0.2)
Chronic obstructive pulmonary disease	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Dyspnoea	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Respiratory failure	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Vascular disorders	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)
Hypertension	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.1)

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (23:05) Source Data: adae Table Generation: 15OCT2021 (14:47)
(Data Cutoff Date: 05OCT2021, Database Snapshot Date: 13OCT2021) Output File: ./nda2_ubBIA/C4591031_A_IA_1/adae_s130_cut_sae_saf

A slightly higher frequency of SAEs was reported in the older (>55 years of age) age subgroups for BNT162b2 and placebo recipients (0.5% vs 0.7%) compared with the younger (16 to 55 years of age) subgroups (0.1% vs 0.3%), without any clinically meaningful imbalance between BNT162b2 and placebo booster recipients within each age group.

The frequencies of SAEs were similar across gender, race, ethnicity, country and SARS-CoV-2 baseline status, without any clinically meaningful imbalance between BNT162b2 and placebo booster recipients.

A total of 5 SAEs (n=3 in the BNT162b2 group and n=2 in the placebo group) were reported as considered by the investigator as related to study intervention. Narratives are summarized below:

A participant **≤24 years of age** in the BNT162b2 group had an SAE of moderate persistent **tachycardia** with onset at 8 days post-booster, reported as **recovered/resolved 2 days after onset**. This event was considered by the investigator as related to study intervention. This participant had a medical history including postural orthostatic tachycardia syndrome and orthostatic hypotension (since 2013). The participant had been seen by a cardiologist prior to study start due to orthostatic hypotension with heart rate acceleration reflective of dehydration and vasovagal presyncope with a structurally normal heart. This participant also reported a non-serious AE of mild intermittent chest pain with onset at 2 days post-booster and reported as ongoing; the investigator assessed this event as related to study intervention. This participant had multiple emergency room visits, which commenced on Study Day 9 due to tachycardia and rapid breathing (occurring 8 hours after receiving an allergy shot); the participant's heart rate was 140 bpm and blood pressure was 145/93 mm Hg. An ECG, chest x-ray, echocardiography, and troponin were all normal. D-dimer was elevated (845 ng/mL; normal: <500 ng/mL), and a chest CT was done to rule out pulmonary embolism, which was normal. The participant was discharged the same day on metoprolol PRN. The participant returned to the emergency room on Day 10 due to tachycardia. The participant's heart rate decreased after taking metoprolol and was treated with ondansetron for vomiting and methylprednisolone due to hives. On Day 11 the participant was evaluated by a cardiologist and had postural tachycardia, which normalized upon sitting. The participant was prescribed increased salt intake, daily metoprolol, and compression stockings. The participant went to the emergency room on Day 12 due to tachycardia and emesis (had stopped metoprolol the day prior due to emesis). The participant was treated with intravenous fluids and anti-emetics. D-dimer was repeated on Day 15 and was 1245. Ultrasound of the lower extremities on Day 53 was normal. On follow-up, the cardiologist reviewed the 2-week cardiac event monitor, and the results were normal.

A participant **55-64 years** of age in the BNT162b2 group had an SAE of moderate **transient elevated hepatic enzymes** with onset at 5 days post-booster. This was identified from a primary care visit with routine laboratory tests. The participant had a medical history including liver disorder, cholecystectomy, diverticulum, hypertension, and drug hypersensitivity. The SAE of transient elevated hepatic enzymes presented as alanine aminotransferase (ALT) of 381 IU/L (normal range [NR]: 0-32 IU/L) and aspartate aminotransferase (AST) of 244 IU/L (NR: 0-40 IU/L). Other pertinent liver function tests (LFTs) included: alkaline phosphatase (ALP) of 236 IU/L (NR: 48-121 IU/L), and total bilirubin of 1.3 mg/dL (NR: 0.0-1.2 mg/dL) with the direct bilirubin of 0.48 mg/dL (NR: 0.00-0.40 mg/dL). The participant felt well and had no symptoms, jaundice, itching, or nausea and did not drink alcohol. On Day 8, the participant was seen by the physician due to a described diverticulitis flare-up that started 2 days prior to Day 1. The participant had taken paracetamol (500 mg PRN/every 6 hours) from Days 1-4. On Day 41, repeat LFTs were performed which showed normal AST, ALT, and ALP (values not reported); however, the bilirubin was still elevated (total bilirubin of 1.8 mg/dL and direct bilirubin of 0.41 mg/dL) that was reported as recovered/resolved at 37 days after onset. This event was considered by the investigator as related to study intervention. This participant had no other AEs after booster vaccination.

A participant **45-54 years** of age in the BNT162b2 group had an SAE of **mild elevated hepatic enzymes** with onset at 49 days post-booster. This event was considered by the investigator as related to study intervention. This participant had a medical history including elevated blood cholesterol and coronary artery disease with coronary artery stent placement, and post-menopausal. On Day 17, the participant started experiencing gagging and choking, stomach distention, left upper quadrant bloating and tenderness, fatigue, and nausea with no loss of smell or taste. During

Days 33-41, the participant experienced increased emesis, dysphagia, and gagging and started to eat only soft food and protein shakes. The participant's symptoms worsened around Day 45, and consulted the primary care physician on Day 49. The laboratory tests were performed on the next day (Day 50). The SAE of elevated hepatic enzymes presented with an elevated ALT of 72 IU/L (NR: 0-32 IU/L), elevated AST of 56 IU/L (NR: 0-40 IU/L), elevated ALP of 160 IU/L (NR: 44-121 IU/L), and total bilirubin of 0.5 mg/dL (NR not reported). All other laboratory test results were normal. On Day 62, the participant's ALT was 163 IU/L (NR: 10-49 IU/L), AST 108 IU/L (NR: <34 IU/L), and ALP 133 IU/L (NR: 48-116 IU/L). The prothrombin time, partial thromboplastin time, bilirubin, and creatine phosphokinase values were within normal limits. Per the participant's primary care physician, the increased hepatic enzymes were deemed to be due to atorvastatin calcium. As a result, the participant was instructed to stop atorvastatin calcium, caffeine, alcohol, and paracetamol. Repeat **laboratory tests on Day 76 noted normalization of ALT/AST/ALP**. This participant had no other AEs after booster vaccination.

A participant **65-74 years** of age in the placebo group had an SAE of **life-threatening acute non-ST elevation myocardial infarction** with onset at 9 days post-booster (placebo), that was reported as **recovered/resolved 4 days after onset.** This event was considered by the investigator as related to study intervention. This participant had a medical history including hypertension, prior tobacco use, overweight, Type II diabetes mellitus, supraventricular tachycardia, and cardiac failure. The participant had received a second dose of the BNT162b2 2-dose primary series and received Dose 3 (placebo) 182 days later. This participant also reported a non-serious AE of mild left arm injection site pain with onset at 1-day post-booster reported as recovered/resolved the next day; the investigator assessed this event as related to study intervention.

A participant **25-34 years of age** in the placebo group had an SAE of **severe chest pain** of unknown aetiology with onset at 6 days post-booster, that was reported as **recovered/resolved on the same day**. This event was considered by the investigator as related to study intervention. This participant had a medical history including supraventricular tachycardia, gastroesophageal reflux disease, and migraine. The participant had received a second dose of the BNT162b2 2-dose primary series and received Dose 3 (placebo) 323 days later. This participant also reported non-serious AEs of mild abdominal pain, nausea, and diarrhoea with onset at 1-day post-booster; and moderate arthralgia of bilateral knees and generalized myalgia with onset at 1-day post-booster. All non-serious AEs were considered by the investigator as related to study intervention, and all were reported as recovered/resolved the day after onset. There was no elevated troponin or ECG change on the emergency room visit to suggest myocarditis; approximately 1 month after the event, the participant completed an echocardiographic study and an exercise stress ECG, which were both normal.

4.2.2.4. Discontinuation from Study Due to Adverse Events

As of the data cut-off date (05 October 2021), 1 participant (55-64-year-old) in the placebo group was withdrawn due to life-threatening SAEs of metastatic cancer with renal, diaphragm, and hepatic involvement. These AEs leading to withdrawal had onset at 51 days post-booster, were ongoing at the time of the data cut-off, and were considered as not related to study intervention.

Additionally, 1 participant in the BNT162b2 group was withdrawn due to a mild pre-vaccination AE of presyncope (vasovagal hypotension) reported 4 days prior to the booster dose that resolved the same day. Note that this participant was screened, presented with AE and failed screening, but was later re-screened and subsequently received a booster vaccination.

4.2.2.5. Pregnancy

From booster vaccination to the data cut-off date (05 October 2021), 1 participant in the placebo group reported exposure during pregnancy resulting in a spontaneous abortion that was reported as an SAE.

4.3. Discussion

The unfavourable effects of vaccination with Comirnaty have been well characterised in clinical trials. The unfavourable effects are mainly AEs associated with reactogenicity that are limited in severity and duration and are fully reversible. Observational data derived from the vaccination campaigns in different countries have generally confirmed this safety profile. Unfavourable effects that have been detected upon the wide-spread use are myo/pericarditis, erythema multiforme and swelling of the vaccinated limb.

The unfavourable effects of a booster administration have been evaluated in the same trial as the immunogenicity of a booster dose (study C4591001, variation EMEA/H/C/005735/II/0067). In individuals 18-55 years of age the safety of a booster dose was regarded as comparable to that of the primary series.

This substudy (C4591031) recruited subjects already included in the phase 3 study (C4591001) that received dose 2 at least 6 months prior. Adverse events were recorded up to one month after the third dose and SAEs will be collected up to 5-6 months after the last dose. No E-diary was used to evaluate reactogenicity. The subjects were randomized to either receive a booster dose of BNT162b2 (30µg) or placebo. Participants randomized to placebo group have now been offered the opportunity to receive BNT162b2 (30µg). The study was executed in Brazil, USA and South Africa.

In total 10,136 subjects were enrolled to the substudy (BNT162b2 n=5,088; placebo n=5,048). Almost all subjects (99.9%) in both the BNT162b2 and the placebo arm received their booster dose and only 0.5% were withdrawn from the study. A majority of the subjects (97%) had a follow-up time of 2-4 months after booster dose up to the cut-off date (05 October 2021). The booster dose was administered 10-12 months after dose 2 in 65% of the participants.

The demographic characteristics of the subjects included in the safety population were generally similar in the BNT162b2 and the placebo group. The majority were white (79%) and most of the participants (86%) were enrolled in the USA. It is noted that many of them (70%) had a BMI suggesting overweight or obesity. The median age were 53 years, and 23% were >65 years of age. About 5% were seropositive to SARS-CoV-2 at baseline.

Among the subjects that received BNT162b2, 25% reported any AEs compared to 7% in the placebo group, most of them were considered nonserious. Any adverse event was with 25.2% reported more often in the group receiving a booster of BNT162b2 30 µg, compared to 6,8% in the placebo group. The most commonly reported SOC was general disorders and administration site conditions (21% vs 3%). The majority of the reported AEs were reactogenicity events, which is illustrated by typical local and systemic reactions more frequently reported among the subjects that received BNT162b2 compared to placebo. For example: injection site pain (12.9% vs. 1.6%), fatigue (7.2% vs. 1.3%), pyrexia (4.8% vs. 0.1%), headache (5.0% vs 1.0%), chills (4.6% vs 0.2%) and myalgia (4.7% vs. 0.4%).

Of note, these numbers are significantly lower to what was reported previously in the phase 2/3 study where the reactogenicity was evaluated by subjects who registered their clinical symptoms on a daily basis during the first 7 days (solicited events). With this study design, the frequencies of reactogenicity events reported as unsolicited events can therefore not be compared to solicited events reported earlier in the phase 2/3 study (C4591001). Reactogenicity data reported by using an E-diary up to 7 days after dose 3 has been reported from 289 subjects aged 18-55 years (study C4591001) that received a booster >5 months after dose 2 (variation EMEA/H/C/005735/II/0067). These results were in line with what has been reported among subjects aged 18-55 years that received Dose 2 in the phase 2/3 study (C4591001), i.e., suggesting a similar reactogenicity profile after dose 2 and 3.

Lymphadenopathy is considered an adverse reaction to vaccination and was reported in 135 subjects that received BNT162b2 and in 2 subjects that received placebo. The intensity was mild to moderate and the event resolved within 3 days after onset. A higher frequency of lymphadenopathy was noted in subjects 18-55 years compared to subjects >55 years of age (4.2% vs 1.0%).

No events of anaphylaxis, hypersensitivity, myocarditis/pericarditis, or Bell's palsy were reported up to the data cut-off date among the subjects that received BNT162b2.

One 45-54-year-old subject reported transient lymphopenia and thrombocytopenia and severe neutropenia with onset 4 days after receiving a booster of BNT162b2. The patient had taken metamizole in high doses shortly after booster vaccination as concomitant medication. Two subjects in the BNT162b2 group reported appendicitis 50 and 70 days after vaccination, none of them considered related to study intervention. Three participants in the BNT162b2 group (vs. 0 in the placebo group) reported events of tachycardia, one of them were reported as SAE (participant ≤24 years) which has resolved.

One subject in the placebo group died due to pulmonary embolism 52 days after receiving the booster dose. None of the subjects in the BNT162b2 group died. Serious AEs were reported at a low frequency (BNT162b2 n=16; placebo n=24). Five (BNT162b2 n=3; placebo n=2) were considered related to study intervention by the investigator. The three cases in the BNT162b2 group included tachycardia and elevated hepatic enzymes, all of them were transient and the subjects have recovered.

The MAH initially proposed to delete the warning in section 4.4 of the SmPC stating that the risk for myocarditis after dose 3 has not been characterized. The data provided in this study can however not be considered sufficient to support such deletion since the population with the highest incidence of myocarditis (male subjects aged <30 years) is too limited to allow characterization of the risk of myocarditis. In response to the request for clarification the MAH agreed not to remove the warning. The myocarditis risk will be addressed in upcoming PSURs.

The MAH was also asked if the lower age limit for the booster dose should be changed to 16 years of age. There are clinical trial data of vaccine booster injections in 46 subjects 16-17 years of age who have been included in the C4591031 substudy and only unsolicited AEs data are available. Results from 289 subjects aged 18-55 years (study C4591001, EMEA/H/C/005735/II/0067) who received a booster >5 months after dose 2 were in line with what was presented for the subjects aged 18-55 years that received Dose 2. Given that the unfavourable effects of the primary series are comparable in adolescents and adults (reactogenicity was slightly higher among adolescents, while adverse events were similar or lower) and given that the unfavourable effects of the booster dose in adults are comparable to that of the primary series, there is no indication that the unfavourable effects of the booster dose in adolescents would be substantially different than the unfavourable effects of the primary series in adolescents.

As regards the characterisation of rare and very rare potentially serious unfavourable effects some observational data are available.

Myocarditis and pericarditis have been observed in younger men more often following the second vaccination of the primary series. From observational data no increase in reporting rate has been described following the booster injection.

5. Changes to the Product Information

As a result of this variation, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC of Comirnaty 30 microgram/dose and section 4.8 of the SmPC of Comirnaty 10 microgram/dose are being updated with efficacy and safety information after booster dose and to change posology recommendations for booster use from "individuals 18 years of age and older" to "individuals 16 years of age and older". The Package Leaflet

and Labelling are updated accordingly.

6. Request for supplementary information

6.1. Other concerns

Clinical aspects

Efficacy

1. Please provide a brief overview of the COVID-19 epidemiological situation in the USA, Brazil and SA during the study period, especially which SARS.COV-2 variants were prevalent in these regions during the study period
2. Please provide the sequencing information of the positive cases at least in the end of the study to show which virus variants were present and if there were any differences of variant distribution between 3 and 2 dose arms.

Safety

1. The MAH has proposed to delete the warning in section 4.4 of the SmPC stating that the risk for myocarditis after dose 3 has not been characterized. The data provided in this study can, however, not be considered sufficient to support such deletion. This is the population with the highest incidence of myocarditis (male subjects aged <30 years) and data is too limited to allow characterization of the risk of myocarditis. The MAH is asked to present how many male subjects aged <30 years have been included in this study (as the only information provided is the number of both male and female subjects <30 years). The proposed deletion is not accepted unless the MAH can present data, mainly based on results from the risk population, that can sufficiently characterize the risk for myocarditis after a third dose. The MAH is invited to comment.
2. The MAH is asked to consider whether the proposed lower age limit of 18 years for the booster dose, might be lowered to 16 years (provided satisfactory responses to the issue of myocarditis), since the study inclusion criteria was subjects from 16 years and older.

7. Assessment of the responses to the request for supplementary information

7.1. Other concerns

Clinical aspects

Question 1

Please provide a brief overview of the COVID-19 epidemiological situation in the USA, Brazil and SA during the study period, especially which SARS.COv-2 variants were prevalent inthese regions during the study period.

Summary of the MAH's response

The enrolment of the study started in July 2021, and the interim analysis was performed in October 2021. Pertinent epidemiological data of this period was slightly different in the United States, Brazil and South Africa, bringing diversity to the study population in terms ofcirculating variants and case rate.

Overall, the three countries showed high rate of new infections during the study period,dominated by the circulating Delta variant.

At the time of the interim analysis, new infection rates started to fall. Delta spread at a highspeed and overtook the Alpha variant, becoming the predominant circulating virus.

United States

In the United States, during the week of 05 July 2021 (beginning of study period), 196% case increase was reported, reaching the highest level of the Delta wave the week of 30 August 2021, with 1,141,955 new cases. The week of 04 October (time of interim analysis), a reduction of 10% was shown and was sustained until 29 November 2021. After this time point, a rise in new infection was associated with the Omicron circulating virus.

According to GISAID, in July 2021, Delta frequency was 79%, but by the time of the interimanalysis, the frequency of Delta reached more than 99%. From 27 December 2021, Omicron became the predominant variant reaching 92%, rising to 96% after 10 January 2022.

Brazil

In Brazil, during the week of 5 July 2021, the number of new infections started to fall, showing 333,030 cases and a weekly decrease of 8.69%. The infection rate continued to dropuntil the week of 20 December 2021, where the lowest number was reported with 21,717 cases. Infections started to rise from the beginning of January 2022 with 476,981 cases during the week of 10 January 2022 and a weekly increase of 193.16% due to Omicron spread.

According to GISIAID, the predominant circulating variant in July 2021 was Gamma (with afrequency of 93%). During the week of 05 July, Delta only represented 5%, Alpha 1% and the rest by other regional variants, including Mu and Lambda. Delta progressed during the study period reaching 94% at the beginning of October 2021. Until the end of November 2021, Delta continued to be the predominant variant (>99%). From the week of 27 December, Omicron overtook Delta and now represents >90%.

South Africa

In South Africa, there was a decrease of new cases from the week of 05 July 2021, with a descending slope during its Delta wave, with 132,986 confirmed cases. It reached a low levelat the beginning of October 2021, with a weekly report of 5,884 cases. The new Omicron wave started after the interim analysis. The week of 22 November 2021, 29,373 cases were reported, as well as a weekly increase of 739.71%.

According to GISIAID, in July 2021, Delta frequency was 90% and Beta frequency was 4%.In early October 2021, the end of the study period, Delta represented 93% and Beta was lower showing 1% of cases. From mid-November 2021, Omicron frequency had a logarithmic rise and reached 88%. Omicron continued to grow, and Delta cut down to 8%.

Assessment of the MAH's response:
According to the MAH, the Delta variant was the most prevalent SARS-CoV-2 variant virus during the study period before first data cut-off at the main study country (USA) and also in South-Africa. At the same time, Gamma was the most prevalent virus variant in Brazil. Therefore, it can be concluded that the vaccine efficacy reported after the first interim analysis is mainly targeted against Delta virus variant.

Conclusion: Issue solved

Question 2
Please provide the sequencing information of the positive cases at least in the end of the study to show which virus variants were present and if there were any differences of variant distribution between 3 and 2 dose arms.

Summary of the MAH's response
Sequencing of all, or a representative sample of, COVID-19 cases will be performed for the end of study analysis. However, it should be noted that following the first interim analysis result, participants were able to be unblinded and the original placebo recipients to receive BNT162b2. It is therefore likely that relatively few 2-dose participants will remain during theOmicron era.

Assessment of the MAH's response
The results of the end of study analysis are awaited.

Conclusion: Issue **not** solved, but not pursued further until the final report of the study is submitted.

Question 3
The MAH has proposed to delete the warning in section 4.4 of the SmPC stating that the risk for myocarditis after dose 3 has not been characterized. The data provided in this study can, however, not be considered sufficient to support such deletion. This is the population with the highest incidence of myocarditis (male subjects aged <30 years) and data is too limited to allow characterization of the risk of myocarditis. The MAH is asked to present how many male subjects aged <30 years have been included in this study (as the only information provided is the number of both male and female subjects <30 years). The proposed deletion is not accepted unless the MAH can present data, mainly based on results from the risk population, that can sufficiently characterize the risk for myocarditisafter a third dose. The MAH is invited to comment.

Summary of the MAH's response
The MAH agrees NOT to delete the warning in section 4.4 of the SmPC stating that the risk for myocarditis after dose 3 has not been characterized.

Assessment of the MAH's response
The response is accepted, however further data is requested (please see below).

Conclusion
Issue resolved

Question 4

The MAH is asked to consider whether the proposed lower age limit of 18 years for the booster dose, might be lowered to 16 years (provided satisfactory responses to the issue of myocarditis), since the study inclusion criteria was subjects from 16 years and older.

Summary of the MAH's response
The MAH has suggested to lower the age limit for a booster dose to 16 years of age. No further data were submitted.

Assessment of the MAH's response
The MAH agrees to lowering the lower age limit for the booster from 18 years to 16 years, since the study inclusion criteria was subjects from 16 years and older.

Conclusion
Issue solved

Question 5

Please include information on the median time from thesecond dose to the booster and the distribution of this parameter in the study description in the SmPC section 5.1.

Summary of the MAH's response
The MAH agrees to include information on the median time from the second dose to the booster and the distribution of this parameter in SmPC Section 5.1. The median time is 10.8 months, with a minimum of 5.0 months and a maximum of 12.6 months.

Assessment of the MAH's response:
MAH has updated the SmPC according to the request

Conclusion:

Issue solved

Question 6
Regarding myocarditis, the MAH is requested to perform a separate analysis of its occurrence in younger males. In this, a comparison between the reported frequency of myocarditis after the third dose (booster) and after the primary vaccination series, as well as to what is expected in an unvaccinated population, should be presented.

Summary of the MAH's response
The MAH presents the below post-authorization data extracted from the PSUR #2 (Section 16.3.1. Evaluation of Important Identified Risks) covering the reporting period of 19 June 2021 through 18 December 2021. The first regulatory approval of a booster dose was granted in the US as an Emergency Use Authorization (EUA) on 12 September 2021. On 05 October 2021, the European Commission (EC) gave a positive opinion (Procedure No. EMEA/H/C/005735/II/0062) for a third dose of the vaccine at least 28 days after the second dose to individuals 12 years of age and older who are severely immunocompromised. The booster approval date occurred during the PSUR reporting period 19 June 2021 through 18 December 2021 (currently under preparation), so although the booster data specify the above reporting interval, they can be considered to be cumulative since the first booster approval

occurred after the DLP of that PSUR. As requested, the data provided are in a younger (<30 years) population. The age groups are separated as follows: <5 years, 5-11 years, 12-15 years, 16-17 years, 18-24 years, 25-29 years and Unknown age (where age was not specified by the reporter). The "Overall – All ages" sub-section includes the above age groups including Unknown age.

While the data provide information on the myocarditis reports received following a booster dose compared with reports following Dose 1 and Dose 2, it is important to note that observed to expected analyses are being prepared for the PSUR #2. These analyses will include myocarditis stratified by Dose 1, 2 and 3 and provide information regarding the ratio of myocarditis AE reports following vaccination with BNT162b2 and a background rate in unvaccinated individuals. In order to evaluate the occurrence of myocarditis with BNT162b2 booster dose administration, the limitations of the post-marketing reporting need to be accounted for. Specifically, the post-marketing data is not suitable for estimation of adverse event frequency. Also, the quality of the post-marketing reports varies, with some reports not providing sufficient information for a meaningful analysis of the event and the vaccine. Data below reflect dose number as reported and/or obtained during follow up, with some cases not reporting the dose that preceded the reported adverse event. The analyses of myocarditis associated with a booster dose of BNT162b2 do not raise significant new safety information.

Important Identified Risks – Myocarditis

Search criteria - PTs: Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis.

Overall - All Ages

• Number of cases: 6347 (1.0% of 657,528 cases of the total PM dataset), compared to 503 cases (0.15%) retrieved in the PSUR #1.
• Country of incidence: Germany (1338), UK (994), Australia (826), France (537), Japan (320), Canada (317), US (215), Italy (211), Sweden (170), and Spain (146). The remaining 1273 cases were distributed among 50 countries.
• Medically Confirmed (3797), Non-Medically Confirmed (2550).
• Subjects' gender: female (2032), male (4022) and unknown (293).
• Subjects' age in years: n = 5615, range: 6-102, mean: 34.3, median: 30.0.
• Medical history (n = 2122): the most frequently (≥50 occurrences) reported medical conditions included hypertension (236), asthma (205), tobacco user (156), seasonal allergy (125), myocarditis (103), drug hypersensitivity (92), obesity (82), hypothyroidism (65), non-tobacco user (64), food allergy (63), migraine (59), alcohol use, chest pain (54 each), diabetes mellitus (50).
• COVID-19 Medical history (n = 331): COVID-19 (168), Suspected COVID-19 (148), SARS-CoV-2 test positive (7), Asymptomatic COVID-19 (4), Coronavirus infection, COVID-19 pneumonia, Post-acute COVID-19 syndrome (3 each), and Exposure to SARS-CoV-2, Occupational exposure to SARS-CoV-2, SARS-CoV-2 antibody test positive (1 each).
• Co-suspects (>1 occurrence): COVID-19 AstraZeneca vaccine (9), COVID-19 Moderna vaccine, influenza vaccine (5 each), acetylsalicylic acid, azathioprine, cannabis sativa, clozapine, colchicine, hepatitis a vaccine, ibuprofen, nivolumab, sulfamethoxazole/trimethoprim (2 each).
• Number of relevant events: 6349.
• Relevant event seriousness: serious (6345), non-serious (4).
• Reported relevant PTs: Myocarditis (6338), Eosinophilic myocarditis (4), Autoimmune myocarditis, Hypersensitivity myocarditis (3 each), Immune-mediated myocarditis (1).
• Relevant event outcome: Fatal (74), resolved/resolving (2618), resolved with sequelae (119), not resolved (1950), unknown (1599).

Age-stratified data

Subjects aged less than 5 years

• Number of cases: No cases were retrieved during the current reporting period; no cases were retrieved in the PSUR #1

Subjects aged 5 - 11 years

• Number of cases: 10 cases (0.002% of 657,528 cases of the total PM dataset; 0.95% of the 1049 subjects aged 5-11 years); 1 case (0.0003%) was retrieved in the PSUR #1.
• Country of incidence: Canada (6), US (2), UK, Vietnam (1 each).
• Subjects' age in years: n = 10, range: 6-9, mean: 8.2, median: 9.0.
• Medical history (n = 4): the reported medical conditions included alopecia universalis, anxiety, attention deficit hyperactivity disorder, drug hypersensitivity, dyspnoea paroxysmal nocturnal, food allergy, mitral valve prolapse, orthopnoea, and renal artery stent placement (1 each).
• COVID-19 Medical history: None.
• Co-suspects: None.
• Most co-reported PTs (>1 occurrence): Chest pain, Product administered to patient of inappropriate age (6 each), Dyspnoea, Fatigue, Pyrexia (3 each), Headache, Off label use, Palpitations, Pericarditis, and Product use issue (2 each)**.**

Myocarditis relevant data in this subgroup of subjects are summarized Table 21.

Table 21. Myocarditis in Subjects aged 5 – 11 Years (N=10)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	2	7	0
	No	0	1	0
Relevant PT[a]	Myocarditis	2	8	0
Hospitalization required/prolonged	Yes	0	4	0
	No	2	4	0
Relevant suspect dose	Dose 1	1	2	0
	Dose 2	0	6	0
	Dose 3	0	**0**	0
	Unknown	1	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=6	≤ 24 hours	0	1	0
	1-5 days	0	3	0
	6-13 days	1	1	0
	14-21 days	0	0	0
	22-31 days	0	0	0
	Unknown	1	3	0
Event Outcome	Fatal	0	0	0
	Not resolved	0	2	0
	Resolved	1	1	0
	Resolved with sequelae	0	0	0
	Resolving	0	0	0
	Unknown	1	5	0
Characteristics		**Female No. of Cases**	**Male No. of Cases**	**Unknown No. of Cases**
Duration of event[b] n=0	Up to 3 days	0	0	0
	4-6 days	0	0	0
	7-25 days	0	0	0

a. All serious occurrences.
b. For those cases where the event resolved.

Subjects aged 12 - 15 years

• Number of cases: 488 (0.07% of 657,528 cases of the total PM dataset; 4.7% of the 10,377 subjects aged 12-15 years), compared to 13 cases (0.004%) retrieved in the PSUR #1.

• Country of incidence: Australia (78), Japan (65), Germany (53), Hong Kong (47), Canada (31), UK (30), France (29), Taiwan Province of China (27), US (16), and Israel (13). The remaining 99 cases were distributed among 25 countries.

• Subjects' age in years: n = 488, range: 12-15, mean: 13.8, median: 14.0.

• Medical history (n = 88): the most frequently (>1 occurrence) reported medical conditions included asthma (15), attention deficit hyperactivity disorder (9), food allergy (6), autism spectrum disorder, cardiac murmur, myocarditis (4 each), allergy to animal, hypersensitivity, mite allergy, pneumonia, rhinitis allergic, seasonal allergy, wheezing (3 each), allergy to arthropod sting, arrhythmia, body height above normal, cardiac murmur functional, chest pain, dermatitis atopic, infectious mononucleosis, intellectual disability, laboratory test abnormal, migraine, nasopharyngitis, scoliosis, vaccination complication, varicella, ventricular tachycardia (2 each).

• COVID-19 Medical history (n = 15): COVID-19 (9), SARS-CoV-2 test positive, Suspected COVID-19 (2 each), Asymptomatic COVID-19, and Exposure to SARS-CoV-2 (1 each).

• Co-suspects: Guanfacine, influenza vaccine live reassort 4V (1 each).

• Most frequently co-reported PTs (>5 occurrence): Chest pain (197), Pyrexia (94), Pericarditis (68), Troponin increased (57), Dyspnoea (56), Palpitations (39), Headache (36), Chest discomfort (31), Tachycardia (29), Fatigue (28), Electrocardiogram ST segment elevation (24), Vomiting (22), Dizziness (20), Blood creatine phosphokinase increased, Malaise (18 each), Troponin T increased (16), Nausea (15), Blood creatine phosphokinase MB increased, Troponin I increased (14 each), Myalgia (12), C-reactive protein increased (10), Electrocardiogram abnormal, Oropharyngeal pain, Pain in extremity (9 each), Cough, Pallor, Pericardial effusion, Troponin abnormal (8 each), Chills, Diarrhoea, Influenza like illness, Pain, Vaccination site pain (7 each), Decreased appetite, Hypotension, and Syncope (6 each).

Myocarditis relevant data in this subgroup of subjects are summarized in Table 22.

Table 22. Myocarditis in Subjects aged 12 – 15 Years (N=488)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	72	302	4
	No	24	84	2
Relevant PTs[a]	Myocarditis	96	386	6
	Hypersensitivity myocarditis	0	1	0
Hospitalization required/prolonged	Yes	44	256	4
	No	52	130	2
Relevant suspect dose	Dose 1	33	93	2
	Dose 2	36	219	2
	Dose 3	1	**0**	0
	Unknown	26	74	2
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=325	≤ 24 hours	6	15	0
	1-5 days	27	210	3
	6-13 days	11	16	0
	14-21 days	8	11	0
	22-31 days	0	8	0
	>31 days	2	8	0
	Unknown	42	119	3
Event Outcome	Fatal	0	3	1
	Not resolved	24	71	1
	Resolved	18	100	0
	Resolved with sequelae	0	3	0
	Resolving	27	114	0
	Unknown	27	96	4
Duration of event[b] n=42, median=5 days	Up to 3 days	0	13	0
	4-6 days	3	12	0
	7-25 days	3	11	0

a. All serious occurrences.
b. For those cases where the event resolved.

Subjects aged 16 - 17 years

• Number of cases: 470 (0.07% of 657,528 cases of the total PM dataset; 6.1% of the 7647 subjects aged 16-17 years), compared to 34 cases (0.01%) retrieved in the PSUR #1.

• Country of incidence: Germany (97), Australia (74), France (40), UK (32), Japan (29), Italy (27), Spain (22), Taiwan Province of China (18), US (15), and Austria (13). The remaining 103 cases were distributed among 29 countries.

• Subjects' age in years: n = 470, range: 16-17, mean: 16.5, median: 17.0.

• Medical history (n = 133): the most frequently (>2 occurrence) reported medical conditions included asthma (20), attention deficit hyperactivity disorder, seasonal allergy (8 each), tobacco user (7), chest pain, rhinitis allergic (6 each), drug hypersensitivity, food allergy, myocarditis, obesity (5 each), acne, dermatitis atopic, hypersensitivity, migraine, non-tobacco user, substance use (4 each), alcohol use, mite allergy (3 each).

• COVID-19 Medical history (n = 17): COVID-19 (9), Suspected COVID-19 (6), Asymptomatic COVID-19, SARS-CoV-2 antibody test positive, SARS-CoV-2 test positive (1 each).

• Co-suspects: Diazepam, lorazepam, meningococcal group ACWY-TT conjugate vaccine, venlafaxine, zopiclone (1 each).

• Most frequently co-reported PTs (>5 occurrence): Chest pain (171), Pyrexia (90), Troponin increased (59), Dyspnoea, Headache (46 each), Pericarditis (34), Fatigue (31), Chest discomfort (27), Myalgia (25), Vomiting (22), Tachycardia (21), Nausea (19), Malaise (17), Inappropriate schedule of product administration, Palpitations (16 each), Electrocardiogram ST segment elevation, Pain in extremity (13 each), Asthenia, Blood creatine phosphokinase increased, Troponin I increased (12 each), Angina pectoris, C-reactive protein increased, Diarrhoea, Pain, Pericardial effusion (11 each), Arthralgia, Chills,

Cough, Paraesthesia (10 each), Oropharyngeal pain (9), Influenza like illness, Troponin T increased (7 each), Decreased appetite, Hypotension, Lethargy, Myocardial necrosis marker increased, and Syncope (6 each).

Myocarditis relevant data in this subgroup of subjects are summarized in Table 23.

Table 23. Myocarditis in Subjects aged 16 – 17 Years (N=470)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	50	291	2
	No	19	106	2
Relevant PT[a]	Myocarditis	69	397	4
Hospitalization required/prolonged	Yes	38	294	0
	No	31	104	4
Relevant suspect dose	Dose 1	26	86	0
	Dose 2	20	219	3
	Dose 3	0	**1**	0
	Unknown	23	91	1
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=349	≤24 hours	4	19	0
	1-5 days	29	185	0
	6-13 days	4	48	1
	14-21 days	3	15	1
	22-31 days	1	16	0
	32-90 days	6	17	0
	Unknown	23	97	2
Event Outcome	Fatal	0	2	0
	Not resolved	21	113	1
	Resolved	14	103	0
	Resolved with sequelae	0	5	0
	Resolving	20	107	1
	Unknown	15	67	2
Duration of event[b] n=54, median=5 days	Up to 3 days	3	13	0
	4-6 days	2	12	0
	7-25 days	3	19	0
	26-31 days	1	1	0

a. All serious occurrences.
b. For those cases where the event resolved.

Subjects aged 18 - 24 years

• Number of cases: 1187 (0.18% of 657,528 cases of the total PM dataset, 2.3% of the 50,779 subjects aged 18-24 years), compared to 120 cases (0.04%) retrieved in the PSUR #1.

• Country of incidence: Germany (256), Australia (180), France (165), UK (117), Italy (54), Japan (49), Sweden (43), Spain (34), US (30), Canada and Denmark (20 each). The remaining 219 cases were distributed among 36 countries.

• Subjects' age in years: n = 1187, range: 18-24, mean: 20.6, median: 20.0.

• Medical history (n = 330): the most frequently (>2 occurrence) reported medical conditions included asthma (44), tobacco user (40), myocarditis (27), seasonal allergy (26), non-tobacco user (16), alcohol use (15), chest pain, drug hypersensitivity (13 each), suppressed lactation (12), attention deficit hyperactivity disorder, depression, migraine, mite allergy, obesity, pericarditis, substance use (9 each), appendicectomy, contraception, nicotine dependence (8 each), food allergy (7), allergy to animal, tonsillectomy, tonsillitis (6 each), anxiety, childhood asthma, dust allergy, dyspnoea, epilepsy (5 each), acne, autism spectrum disorder, Crohn's disease, Gilbert's syndrome, irritable bowel syndrome, rhinitis allergic, type 1 diabetes mellitus (4 each), adenotonsillectomy, circulatory collapse, cough, diarrhoea, familial risk factor, glucose-6-phosphate dehydrogenase deficiency, nasopharyngitis, and tobacco abuse (3 each).

• COVID-19 Medical history (n = 55): COVID-19 (37), Suspected COVID-19 (15), SARS-CoV-2 test positive (2), Asymptomatic COVID-19, Coronavirus infection (1 each).

• Co-suspects: Clozapine, colchicine, COVID-19 AstraZeneca vaccine (2 each), cannabis sativa, COVID-19 Moderna vaccine, hepatitis A vaccine, ibuprofen, influenza vaccine (1 each).

• Most frequently co-reported PTs (>10 occurrence): Chest pain (412), Pyrexia (192), Dyspnoea (157), Troponin increased (152), Chest discomfort (122), Pericarditis (96), Palpitations (89), Fatigue (88), Headache (80), Tachycardia (54), Pain (48), Chills (45), Electrocardiogram ST segment elevation (42),

Inappropriate schedule of product administration, Myalgia (41 each), Malaise (40), Nausea (37), Off label use (36), Dizziness, Pain in extremity (33 each), Influenza like illness (32), C-reactive protein increased (31), Arthralgia (28), Asthenia, Interchange of vaccine products (27 each), Pericardial effusion (26), Diarrhoea (24), Blood creatine phosphokinase increased, Cough (23 each), Vomiting (22), Arrhythmia (21), Electrocardiogram abnormal, Immunisation (20 each), Troponin T increased (19), Heart rate increased (18), Angina pectoris, Hyperhidrosis, Oropharyngeal pain (16 each), Lethargy (15), Disease recurrence, Myocardial necrosis marker increased (14 each), Dyspnoea exertional, Paraesthesia, Syncope, Troponin I increased (13 each), Cardiac failure, Vaccination site pain (12 each), COVID-19, Lymphadenopathy, Pleuritic pain (11 each).

Myocarditis relevant data in this subgroup of subjects are summarized in Table 24.

Table 24. Myocarditis in Subjects aged 18 – 24 Years (N=1187)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	158	642	3
	No	82	295	7
Relevant PT(s)[a]	Myocarditis	239	934	10
	Autoimmune myocarditis	1	1	0
	Hypersensitivity myocarditis	0	2	0
Hospitalization required/prolonged	Yes	111	658	6
	No	129	281	4
Relevant suspect dose	Dose 1	75	211	4
	Dose 2	76	524	3
	Dose 3	7	**18**	0
	Unknown	82	184	3
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=875	≤24 hours	17	38	1
	1-5 days	76	469	5
	6-13 days	21	96	2
	14-21 days	13	40	0
	22-31 days	9	30	0
	32-60 days	11	28	0
	61-232 days	3	16	0
	Unknown	90	227	2
Event Outcome	Fatal	1	1	0
	Not resolved	81	255	3
	Resolved	47	187	1
	Resolved with sequelae	4	13	0
	Resolving	65	328	3
	Unknown	42	159	3
Duration of event[b] n=95, median=5 days	Up to 3 days	9	17	0
	4-6 days	4	28	1
	7-25 days	4	25	0
	26-86 days	2	5	0

a. All serious occurrences.
b. For those cases where the event resolved.

Subjects aged 25 - 29 years

• Number of cases: 589 (0.09% of 657,528 cases of the total PM dataset, 1.0% of the 58,731 subjects aged 25-29 years), compared to 55 cases (0.02%) retrieved in the PSUR #1.

• Country of incidence: Germany (137), Australia (96), UK (95), France (56), Italy (24), Finland (20), Japan (18), Sweden (15), Canada (13), Austria, Belgium, and Spain (12 each). The remaining 79 cases were distributed among 29 countries

• Subjects' age in years: n = 589, range: 25-29, mean: 26.9, median: 27.0.

• Medical history (n = 193): the most frequently (>2 occurrence) reported medical conditions included tobacco user (22), asthma (15), seasonal allergy (14), myocarditis (13), drug hypersensitivity (10), alcohol use, food allergy, non-tobacco user, suppressed lactation (9 each), obesity (7), migraine (6), pericarditis (5), attention deficit hyperactivity disorder, drug dependence, dyspnoea, nicotine dependence, palpitations, polycystic ovaries (4 each), abstains from recreational drugs, allergy to animal,

anxiety, appendicectomy, breast feeding, cardiac disorder, chest pain, colitis ulcerative, depression, drug abuse, endometriosis, ex-tobacco user, hypersensitivity, immunodeficiency, irritable bowel syndrome, mite allergy, oropharyngeal pain, pyrexia, substance use, and type 1 diabetes mellitus (3 each).

• COVID-19 Medical history (n = 33): COVID-19 (19), Suspected COVID-19 (14), Occupational exposure to SARS-CoV-2, and Post-acute COVID-19 syndrome (1).

• Co-suspects: COVID-19 Moderna vaccine, diphtheria vaccine toxoid/ pertussis vaccine acellular/ tetanus vaccine toxoid, ibuprofen, and sumatriptan (1 each)

• Most frequently co-reported PTs (>10 occurrence): Chest pain (197), Dyspnoea (111), Pyrexia (89), Palpitations (80), Pericarditis (73), Fatigue (68), Chest discomfort (64), Troponin increased (56), Headache (47), Tachycardia (46), Asthenia, Dizziness, Malaise (28 each), Nausea, Pain (26 each), Inappropriate schedule of product administration, Myalgia, Pain in extremity, Pericardial effusion (25 each), Arrhythmia (23), Chills (22), Angina pectoris (21), Arthralgia (20), Heart rate increased (19), Syncope (17), Paraesthesia (15), Immunisation (13), Vomiting (12), Cough, Hyperhidrosis, Off label use (11 each).

Myocarditis relevant data in this subgroup of subjects are summarized in Table 25.

Table 25. Myocarditis in Subjects aged 25 – 29 Years (N=589)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	79	254	1
	No	83	167	5
Relevant PT(s)[a]	Myocarditis	162	420	6
	Autoimmune myocarditis	0	1	0
Hospitalization required/prolonged	Yes	60	252	2
	No	102	169	4

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Relevant suspect dose	Dose 1	54	104	3
	Dose 2	61	212	0
	Dose 3	7	**5**	1
	Unknown	40	100	2
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=392	≤ 24 hours	13	29	1
	1-5 days	45	155	1
	6-13 days	18	40	0
	14-21 days	2	29	0
	22-31 days	9	11	0
	32-60 days	9	17	0
	61-111 days	3	10	0
	Unknown	63	130	4
Event Outcome	Fatal	1	6	0
	Not resolved	69	130	3
	Resolved	17	77	0
	Resolved with sequelae	6	6	0
	Resolving	38	128	0
	Unknown	31	74	3
Duration of event[b] n=41, median=5 days	Up to 3 days	3	10	0
	4-6 days	1	8	0
	7-25 days	2	11	0
	26-165 days	1	5	0

a. All serious occurrences.
b. For those cases where the event resolved.

Subjects with Unknown Age

• Number of cases: 732 (0.11% of 657,528 cases of the total PM dataset, 0.97% of the 74704 subjects with unknown age), compared to 26 cases (0.01%) retrieved in the PSUR #1.

• Country of incidence: Germany (165), Canada (154), UK (149), Hong Kong (53), US (48), Australia (41), Japan (34), Greece (17), Brazil (12), France (9). The remaining 50 cases were distributed among 26 countries.

• Subjects' age in years (n = 732): Unknown

• Medical history (n = 146): the most frequently (≥6 occurrences) reported medical conditions included asthma (21), hypertension (13), anxiety (12), depression, SARS-CoV-2 test negative (9 each), immunodeficiency, seasonal allergy (8 each), attention deficit hyperactivity disorder, drug hypersensitivity, food allergy, hypothyroidism (7 each), and diabetes mellitus (6).

• COVID-19 Medical history (n = 40): Suspected COVID-19 (28), COVID-19 (11), SARS-CoV-2 test positive (2).

• Co-suspects: amoxicillin, emtricitabine/tenofovir disoproxil, propranolol, ramipril, and varenicline (1 each).

• Most frequently co-reported PTs (>10 occurrence): Chest pain (173), Pericarditis (119), Dyspnoea (109), Fatigue (91), Palpitations (82), Pyrexia (77), Tachycardia (49), Immunisation (46), Chest discomfort (44), Off label use (34), Headache (31), Pain in extremity (29), Chills, Interchange of vaccine products, Nausea (25 each), Myalgia (21), Malaise, Pain (20 each), COVID-19, Dizziness (19 each), Asthenia, Back pain, Cough, Inappropriate schedule of product administration (17 each), Drug ineffective, Vomiting (16 each), Diarrhoea (14), Arthralgia, Hyperhidrosis, Hypoaesthesia (13 each), Syncope (12), and Angina pectoris (11).

Myocarditis relevant data in this subgroup of subjects are summarized in Table 26.

Table 26. Myocarditis in Subjects of Unknown Age (N=732)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	83	199	171
	No	99	120	60
Relevant PT[a]	Myocarditis	182	319	231
Hospitalization required/prolonged	Yes	53	144	14
	No	129	175	217
Relevant suspect dose	Dose 1	59	102	17
	Dose 2	69	131	24
	Dose 3	22	17	10
	Unknown	32	69	180
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=157	≤24 hours	4	7	2
	1-5 days	19	60	3
	6-13 days	12	14	0
	14-21 days	5	9	1
	22-31 days	2	6	1
	32-72 days	3	9	0
	Unknown	138	216	224
Event Outcome	Fatal	1	5	3
	Not resolved	54	107	12
	Resolved	36	72	9
	Resolved with sequelae	3	3	0
	Resolving	18	19	4
	Unknown	70	115	203
Duration of event[b] n=6, median=4 days	Up to 3 days	1	0	1
	4-6 days	1	1	1
	7-27 days	0	1	0

a. All serious occurrences.
b. For those cases where the event resolved.

Subjects with booster dose

• Number of cases: 381 (0.06% of 657,528 cases of the total PM dataset, 1.5% of the 25787 subjects who received a booster dose), compared to no cases in the PSUR #1.

• Country of incidence: UK (303), Israel (18), Germany (17), France (9), Italy (8), US (6), Sweden (4), Austria, Brazil, Denmark, Norway (2 each). The remaining 8 cases were distributed among 8 countries.

• MC (102), NMC (279).

• Subjects' gender: female (209), male (157), and unknown (15).

• Subjects' age in years: n = 332, range: 13-90, mean: 52.1, median: 53.0.

• Medical history (n = 94): the medical conditions reported (>4 occurrence) included hypertension (15), immunodeficiency (15), type 2 diabetes mellitus (7), depression (6), anxiety, asthma, fibromyalgia, influenza immunization, neoplasm, and rheumatoid arthritis (5 each).

• COVID-19 Medical history (n = 27): Suspected COVID-19 (21). COVID-19 (6), Post-acute COVID-19 syndrome (1).

• Co-suspects (n=13) reported more than once: influenza vaccine (5), hepatitis A vaccine (2).

• Number of relevant events: 381.

• Relevant event seriousness: all serious.

• Reported relevant PTs: Myocarditis (381).

• Relevant event outcome: fatal (4), resolved/resolving (83); resolved with sequelae (2), not resolved (93), unknown (200).

• Most frequently co-reported PTs (>20 occurrence): Immunisation (359), Off label use (243), Fatigue (194), Interchange of vaccine products, Pericarditis (173 each), Chest pain (168), Palpitations (157), Dyspnoea (147), Tachycardia (120), Pyrexia (104), Headache (59), Arthralgia (34), Chest discomfort, Chills, Dizziness, Pain in extremity (31 each), Nausea (29), Asthenia (27), Malaise, Pain (26 each), Myalgia (23), and Syncope (21).

The number of myocarditis cases occurred after a booster dose in each age group is reported in Table 27.

Table 27. Myocarditis in Subjects who Received a Booster dose

Characteristics		Heterologous Booster dose No. of Cases			Homologous Booster dose No. of Cases		
		F	M	U	F	M	U
Age group	0 to 17 years	0	0	0	1	1	0
	18 to 24 years	2	7	0	5	13	0
	25 to 29 years	2	3	0	5	3	1
	30 to 39 years	15	6	1	12	7	0
	40 years and older	84	64	2	61	36	1
	Unknown	9	9	3	13	8	7
	TOTAL	112	89	6	97	68	9

F=female; M=male; U=unknown.
Grey shadowed cells are not of interest for the purpose of this response, but they are kept for consistency with content of the PSUR #1.

Cases Medically Confirmed with a Time To Onset ≤ 21 Days: 2007 Cases

These 2007 cases were individually reviewed and assessed according to BC Myocarditis Case Definition and Level of Certainty Classification (version 1.5.0, 16 July 2021), as per table below:

Table 28. Cases Medically Confirmed with a Time To Onset ≤ 21 Days: 2007 Cases

Age group	Brighton Collaboration Level[a] (No. of Cases)				
	1	2	3	4	5
5-11	0	0	0	6	0
12-15	28	41	6	167	7
16-17	46	22	2	151	3
18-24	82	67	10	336	12
25-29	32	20	2	133	3
30-39[b]	38	21	3	198	11
40+ [b]	48	39	11	352	10
Unknown	1	2	0	96	1
Total	*275*	*212*	*34*	*1439*	*47*
Total[c]	***189***	***152***	***20***	***889***	***26***

a. Level 1 indicates a definitive case (i.e. it includes criteria for the highest level of diagnostic certainty of myocarditis), Level 2 indicates a probable case, and Level 3 indicates a possible case; Level 4 is defined as "reported event of myocarditis with insufficient evidence to meet the case definition" and Level 5 as not a case of myocarditis.
b. Grey shadowed cells are not of interest for the purpose of this response, but they are kept for consistency with content of the PSUR #2.
c. Excluding 30-39 and 40+

Out of the 189 BC level 1 cases reported in the population aged less than 30 years, 166 of them occurred in male subjects. Demographic information on male cases aged less than 30 years assessed as BC Level 1

- Number of cases: 166
- Number of events: 166 coding to the PT Myocarditis (165) and Hypersensitivity myocarditis (1).
- Country of incidence (>2 occurrences): France (74), Spain (22), Japan (11), Germany, Italy and UK (7 each), Czech Republic and Switzerland (5 each), Denmark and Sweden (4 each), Belgium, Finland and Netherlands (3 each), Greece and Hungary (2 each) and 1 each from other 7 countries.
- Subjects' age in years: n = 165, range 12 – 29, mean 19.7, median 19.0.
- Medical history (n=85): medical conditions reported in at least 5 cases included tobacco user (21), myocarditis (10), substance use (9), asthma (8), seasonal allergy and alcohol use (5 each).
- Time to event onset (n=166):
    - o <24 hours: 9 events,
    - o 1-5 days: 120 events,
    - o 6-13 days: 23 events,
    - o 14-21 days: 14 events.
- Duration of relevant events (n = 25):
    - o Up to 3 days: 3 events,
    - o 4-6 days: 9 events,
    - o 7-26 days: 13 events.
- Most frequently co-reported PTs (≥10 occurrences): Chest pain (71), Pyrexia (40), Headache (17), Dyspnoea (16), Troponin increased (15), Electrocardiogram ST segment elevation (14), Pericarditis (12), Chest discomfort and Influenza like illness (11 each).
- Relevant event outcome: fatal (2), resolved/resolving (133), resolved with sequelae (3), not resolved (23) and unknown (5).

Assessment of the MAH's response

Age specific cases with Myocarditis following vaccination are presented for age groups 0-5, 5-11, 12-15, 16-17, 18-24, 25-29 years of age. There were no cases in the age group below 5 years of age and 10 cases are detected in the age group 5-11 years of age. In age groups older than 11 years of age (12-15, 16-17, 18-24, 25-29) most cases are reported in males and after second dose.

No data on the total number of administered doses or in each age group are presented, being therefore difficult to estimate the frequency of reported cases of Myocarditis overall, in each age group and stratified after the respective dose.

A review of all reported cases of Myocarditis (n=2007) with TTO < 21 days is presented. Out of these, 189 were assessed as Myocarditis Brighton Criteria level 1 cases reported in the population aged less than 30 years, 166 of them occurred in male subjects and most of them having a TTO 1-5 days (120 events). Also subjects in all ages with Myocarditis after receiving booster dose (n = 381; female (209), male (157), and unknown (15)) are separately presented.

Conclusion

The presented data are generally in agreement with previously assessed data, with a predominance of cases reported among younger males following dose 2.

The absolute number of observed Myocarditis cases in younger individuals after dose three is up to now small. At the current time it can be assumed that the number of younger individuals exposed to a booster dose is likely to be relatively low, but no data on this issue has been presented in this report. Thus, at this stage presented post-marketing data do not allow to draw a final conclusion on the risk of myocarditis among younger subjects, especially after the third dose. However, the MAH has suggested to present a full analysis of dose stratified data in PSUR#2, which is supported.

As discussed in Question 3 the MAH has agreed not to delete the warning in section 4.4 of the SmPC stating that the riskfor myocarditis after dose 3 has not been characterized, which is also supported.

Issue not further pursued in this assessment report, but in the upcoming PSUR#2.

Conclusion:

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

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

COVID-19 is an infectious disease caused by a newly discovered coronavirus, SARS-CoV-2, which appeared in the Wuhan province in China in 2019 and has spread world-wide during 2020 ever since, causing WHO to declare a pandemic on 11 March 2020. The virus infects primarily the airways and causes a broad spectrum of respiratory infections from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS). The pandemic is ongoing despite unprecedented efforts to control the outbreak.

COVID-19 in adolescents is mostly a mild disease. Severe cases occur rarely, and predominantly in subjects with underlying conditions. Several different variants of SARS-CoV-2 have been circulating since the outbreak started, with the omicron variant being the dominant variant at the present time. Analysis of antibody titres of vaccinated adults have shown that the titres of neutralising antibodies to the omicron variant of SARS-CoV-2 are considerably lower when compared to the titres to the Wuhan-based strain included in the vaccine. Observational data also indicate that in adults the vaccine effectiveness to the omicron variant is lower. This effectiveness to the omicron variant can be increased by administration of a booster dose.

There are currently no vaccines against COVID-19 approved for the use as a booster in adolescents.

The current variation is based on interim results from study C4591031, which is a randomized, placebo-controlled, phase 3 booster efficacy study involving participants ≥ 16 years of age who completed the primary series of BNT162b2 30 µg in Study C4591001. The purpose of this type II variation is to update

the product information with updated data from the continuation study of the pivotal study to estimate the efficacy and safety of the booster dose.

In total 10,136 subjects were enrolled to the substudy (BNT162b2 n=5,088; placebo n=5,048). Almost all subjects (99.9%) in both the BNT162b2 and the placebo arm received their booster dose and only 0.5% were withdrawn from the study. A majority of the subjects (97%) had a follow-up time of 2-4 months after the booster dose up to the cut-off date (05 October 2021). The booster dose was administered 10-12 months after dose 2 in 65% of the participants. The median age was 53 years, and 23% were >65 years of age. 46 subjects receiving Comirnaty and 44 receiving placebo were 16-17 years old.

It was originally intended that all participants would remain blinded until the outcome of the protocol prespecified data analysis had been reviewed by the Data Monitoring Committee (DMC), that was planned to be conducted once all participants reached 2 months after booster vaccination. However, considering the observation of waning effectiveness and recommendation for booster doses in some countries, per the protocol, participants could be unblinded from 24 September 2021 onwards, and those who had been randomized to receive Dose 3 of placebo were offered a dose of BNT162b2 30 µg in order to receive a booster of active vaccine. At the time of this analysis, some (but not all) participants have been unblinded per protocol; the analyses take account of this, as individual participant data are censored at the time of their unblinding.

The Delta variant was the most prevalent SARS-CoV-2 variant virus in the study in the USA and South-Africa; the Gamma variant was the most prevalent virus variant in Brazil. Therefore, it can be concluded that the vaccine efficacy reported after the first interim analysis is mainly targeted against the Delta virus variant.

The relative vaccine efficacy of three doses in the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days post-booster was observed as 95.3% (2-sided 95% CI: 89.5%, 98.3%), based on 6 cases in the BNT162b2 group and 123 cases in the placebo group. The relative VE was very similar in the evaluable efficacy population with or without evidence of SARS-CoV-2: 94.6% (2-sided 95% CI: 88.5%, 97.9%), based on 7 cases in the BNT162b2 group and 124 cases in the placebo group.

For all subgroups analysed including demographics, country, time interval between Dose 2 and the booster dose, and risk status, the confirmed COVID-19 cases were predominantly reported in the placebo group. The estimated vaccine efficacy for most subgroups was >90%. Signs and symptoms associated with COVID-19 cases were fewer and milder in the 3-dose arm compared to the 2-dose arm.

It is noted that the inclusion criteria of the study had a lower age limit of 16 years of age. On this basis, the MAH was invited to discuss an indication for the booster spanning also those aged 16-17 (the booster is presently approved for adults, based on immunogenicity and reactogenicity data).

It is likely that protection following a booster dose is no less in the 16-17 years old compared to older subjects. Immune responses are generally higher in younger subjects compared to older subjects. The relative efficacy not only takes the protection following the booster dose into account, but also the remaining efficacy of the two primary doses, i.e. assuming that protection wanes slower in younger subjects, the relative efficacy of a third dose would be lower compared to that in older subjects.

Regarding safety, among the subjects that received BNT162b2 30 µg, 25% reported any AEs compared to 7% in the placebo group, most of them were considered nonserious. The most commonly reported SOC was general disorders and administration site conditions (21% vs 3%).

A vast majority of the reported AEs were reactogenicity events, which is illustrated by typical local and systemic reactions more frequently reported among subjects that received BNT162b2 compared to

placebo. For example: injection site pain (12.9% vs. 1.6%), fatigue (7.2% vs. 1.3%), pyrexia (4.8% vs. 0.1%), headache (5.0% vs 1.0%), chills (4.6% vs 0.2%) and myalgia (4.7% vs. 0.4%).

Of note, these numbers are considerably lower to what was reported previously in the phase 2/3 study where reactogenicity was evaluated by subjects who registered their clinical symptoms on daily basis during the first 7 days. In the current study, daily reporting of reactogenicity was made only in a small subset, and the frequencies of reactogenicity events reported as unsolicited events can therefore not be compared to solicited events reported earlier in the phase 2/3 study (C4591001).

Reactogenicity data have previously been reported by using an E-diary up to 7 days after dose 3 from 289 subjects aged 18-55 years (study C4591001) who received a booster >5 months after dose 2 (EMEA/H/C/005735/II/0067). The results from that study were in line with what has been reported among subjects aged 18-55 years that received Dose 2 in the phase 2/3 study (C4591001), i.e., suggesting a similar reactogenicity profile after dose 2 and 3.

Lymphadenopathy is considered an adverse reaction to vaccination, included in the product information and was reported in 135 subjects that received BNT162b2 and in 2 subjects that received placebo. The intensity was mild to moderate and the events resolved within 3 days after onset. A higher frequency of lymphadenopathy was noted in subjects 18-55 years compared to subjects >55 years of age (4.2% vs 1.0%).

No events of anaphylaxis, hypersensitivity, myocarditis/pericarditis, or Bell's palsy were reported up to the data cut-off date among subjects that received BNT162b2.

The MAH had proposed to delete the warning in section 4.4 of the SmPC stating that the risk for myocarditis after dose 3 has not been characterized. In response to the request for clarification and to submit further data to substantiate that this risk has been characterised, the MAH agreed not to remove the warning, as further data are not available.

As mentioned above, the MAH was also asked if the lower age limit for the booster dose should be changed to 16 years of age. The ability of Comirnaty to boost the vaccine-induced immune response has been demonstrated in adults 18 to 55 years of age. Although the submitted clinical data of a booster dose in adolescents is limited, it is considered appropriately justified to update the Comirnaty 30 microgram/dose SmPC to lower the age of the booster dose from adults 18 years of age and older to adults and adolescents 16 years of age and older. Comirnaty has been shown to be at least as good at inducing neutralising antibody titers after the primary series in adolescents as in adults, and while the ability to boost the vaccine-induced immune response was only shown in adults, a booster response to the vaccine can equally be expected in adolescents. Further, in view of the overall similarity of the safety profile of the primary vaccine regimen between adolescents and healthy adults, and the fact that the booster dose in adults is not more reactogenic than the second dose, it can be extrapolated that no particular safety concerns with the booster dose in adolescents are to be expected.

It has been shown in adults that the administration of a booster dose is able to induce titres of neutralising antibodies. Observational data confirm that effectiveness against symptomatic disease due to the omicron variant can indeed be increased by the booster injection. Based on the above, it is justified that if protection induced by the primary schedule needs to be recovered in adolescents, due to either waning antibodies or emergence of new variants, a booster dose can be administered. There are no reasons to believe that the administration of a booster to adolescents 16-17 years results in antibody titres that are inferior to the titres observed in adults.

The benefit-risk balance of COMIRNATY, remains positive.

9. Recommendations

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

Variation requested		Type	Annexes affected
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, IIIA and IIIB

Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC of Comirnaty 30 microgram/dose and section 4.8 of the SmPC of Comirnaty 10 microgram/dose in order to update efficacy and safety information after booster dose and to change posology recommendations for booster use from "individuals 18 years of age and older" to "individuals 16 years of age and older", based on interim results from study C4591031, this is a randomized, placebo-controlled, phase 3 booster efficacy study involving participants ≥ 16 years of age who completed the primary series of BNT162b2 30 µg in Study C4591001, published literature data and post-marketing safety data. The Package Leaflet and Labelling are updated accordingly.

In addition, the MAH took the opportunity to make minor editorial changes throughout the product information.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIA and IIIB are recommended.

[i] Food and Drug Administration. Development and licensure of vaccines to prevent COVID-19. Available at: https://www.fda.gov/media/139638/download. Accessed: 27 Apr 2021.

[ii] Centers for Disease Control and Prevention. People with certain medical conditions. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed: 27 Apr 2021.