EMA/890825/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/005735/II/0129

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	16 May 2022
CHMP Rapporteur Assessment Report	09 Jun 2022
CHMP members comments	10 Jun 2022
ETF meeting	14 Jun 2022
Updated CHMP Rapporteur Assessment Report	17 Jun 2022
Request for Supplementary Information	23 Jun 2022
Re-start of procedure	17 Aug 2022
CHMP Rapporteur Assessment Report	31 Aug 2022
CHMP members comments	02 Sep 2022
ETF meeting	06 Sep 2022
Updated CHMP Rapporteur Assessment Report	06 Sep 2022
Opinion	15 Sep 2022

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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 12 May 2022 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 and IIIB

Update of sections 4.2, 4.8 and 5.1 of the SmPC of COMIRNATY 10 µg Concentrate for dispersion for injection in order to introduce a booster dose for children 5 to 11 years of age based on interim results from study C4591007 listed as a specific obligation in the Annex II; this is a Phase 1, Open-Label Dose-Finding Study to Evaluate Safety, Tolerability, and Immunogenicity and Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate Against COVID-19 in Healthy Children and Young Adults; the Package Leaflet is updated accordingly.

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 and Package Leaflet.

2. Introduction

Comirnaty booster evaluations are ongoing in Study C4591001 (adult), Study C4591007 (pediatric), and C4591031 (adult and adolescent). For individuals ≥12 years of age, the BNT162b2 30-µg was selected following review of immunogenicity and safety data from Phase 1 of Study C4591001 as well as nonclinical data. This dose and construct provided the optimum combination of a favorable reactogenicity profile and a robust immune response likely to afford protection against COVID-19.

For individuals <12 years of age, pediatric Study C4591007 used a Phase 1 age de-escalation strategy to select the most appropriate dose level of BNT162b2. Review of Phase 1 safety (primarily reactogenicity) and immunogenicity data led to the selection of BNT162b2 10-µg for children 5 to <12 years of age and 3-µg for children 6 months to <5 years of age, in order to balance the best observed tolerability and robust immune responses.

Clinical data from these studies, along with available real-world safety and effectiveness data, were previously submitted to support the current authorization of BNT162b2 as:

Two-dose series: Conditional marketing approval was granted by the European Medicines Agency (EMA) on 21 December 2020 for administration of the two-dose series of BNT162b2 30-µg to individuals ≥16 years of age and expanded to include use in individuals ≥12 years of age on 28 May 2021; the indication was expanded on 25 November 2021 to include a two-dose series of BNT162b2 10-µg to individuals 5 through 11 years of age. Conditional marketing approval was granted on 03 November 2021 for a manufacturing change to include an additional formulation of the vaccine that uses Tris buffer instead of PBS (30-µg and 10-µg dosage strengths).

Third dose: Conditional marketing approval was granted on 05 October 2021 for a third dose of BNT162b2 30-µg to be administered ≥28 days after the second dose to individuals ≥18 years of age with severe immunocompromise and extended on 05 October 2021 to include a third dose of BNT162b2 10-µg

to be administered ≥28 days after the second dose to individuals 5 to <12 years of age with severe immunocompromise.

Booster: Conditional marketing approval was granted on 05 October 2021 for a booster dose of BNT162b2 30-µg to be administered ≥6 months after completing the primary series to individuals ≥18 years of age, and extended on 24 February 2022 to include booster administration to individuals ≥12 years of age.

Current submission presents clinical data from ongoing pediatric Study C4591007, in support of a booster (third) dose of BNT162b2 10-µg in children 5 to <12 years of age.

3. Clinical Efficacy aspects

Phase 1/2/3 Study C4591007

Study C4591007 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 study including healthy children from 6 months to <12 years of age. The study was designed to evaluate BNT162b2 vaccination in an age de-escalation Phase 1 dose finding part and Phase 2/3 selected dose part, in protocol defined age groups: 5 to <12 years, 2 to <5 years, and 6 months to <2 years of age.

Phase 2/3 commenced at the selected vaccine dose level, with participants randomized 2:1 to receive vaccine or placebo, and conducted at sites in the US, Finland, Poland, and Spain. The primary series of BNT162b2 was initially planned as a two-dose series; however, based on emerging clinical and real-world data, the protocol was amended to add a third dose at the selected dose level for each age group.

Phase 1 and Phase 2/3 data from the 5 to <12 years of age group following the two-dose vaccine series were previously submitted. The current submission includes safety and immunogenicity data following a booster (third) dose of BNT162b2 10-µg administered to Phase 2/3 study participants 5 to <12 years of age.

Unblinding Considerations

Not applicable for children 5 to <12 years of age who, per protocol, could be unblinded to treatment assignment at 6 months after Dose 2 (which either preceded or coincided with timing of Dose 3 administration).

In general, sponsor and site personnel responsible for the ongoing conduct of Phase 2/3 Study C4591007 remain blinded to individual randomization until a participant or study is unblinded per protocol. Serology samples are processed in a blinded manner by laboratory personnel. A separate (from study conduct) unblinded submissions team is responsible for regulatory submissions.

Specifically, after discussion with regulatory authorities, participants 5 to <12 years of age in Study C4591007 originally randomized to receive two doses of BNT162b2 or placebo were eligible to be unblinded according to local eligibility to receive a COVID-19 vaccine available under emergency use or conditional marketing authorization (since October 2021); or they could be unblinded when they reached 6 months of follow-up post-Dose 2, in accordance with the study protocol. Note that the protocol specified timing of booster vaccination for participants 5 to <12 years of age was ≥6 months after Dose 2); therefore, booster (third) doses have been administered to participants in this age group in an open-label manner. Participants in the study will continue to be followed in an open-label observational manner until the end of the study.

3.1. Methods – analysis of data submitted

Vaccine efficacy was previously evaluated in Phase 2/3 of registrational Study C4591001 and for the 5 to <12 years of age population in pediatric Study C4591007. Immunogenicity data were previously evaluated in Phase 1 and Phase 2 of Studies C4591001 and C4591007. These data were previously submitted to support current indications.

The basis of demonstrating BNT162b2 effectiveness in children is immune response data. Immunogenicity data include SARS-CoV-2 neutralizing titers against the wild-type strain and Omicron variant after a booster (third) dose of BNT162b2 10-µg, up to 1-month post-Dose 3.

3.2. Immunogenicity Endpoints

Immunogenicity analyses were conducted for an immunogenicity set of participants based on all-available and evaluable immunogenicity populations. The immunogenicity set was comprised of:

3-Dose set: included up to 130 participants who received Dose 3 and completed the 1-month post-Dose 3 visit prior to 15 March 2022. Within this set, up to 30 participants also had blood sample collection at 1-month post-Dose 2; sera from these participants were also analyzed for Omicron neutralization.

2-Dose set: included up to 70 additional participants randomly selected from the previously analyzed Dose 2 evaluable immunogenicity population who were without evidence of prior infection up to 1-month post-Dose 2 (ie, included in the two-dose immunobridging analysis). These additional participants were included to ensure sufficient post-Dose 2 data for analyses.

The Dose 2 and Dose 3 evaluable immunogenicity populations included participants who received all doses of vaccine at the same dose level as randomized (ie, two or three doses) within the protocol specified window for each dose, had ≥1 valid and determinate immunogenicity result within 28-42 days after vaccination, and did not have any important protocol deviations impacting evaluability.

Data were analyzed combining the available assay results from the 2-dose set and 3-dose set to evaluate immune responses at each time point. A separate summary for participants in the 3-dose set with assay results at both 1-month post-Dose 2 and 1-month post-Dose 3 was also provided. Analyses were conducted for participants either without, or with or without, evidence of prior SARS-CoV-2 infection up to 1-month post-Dose 2 or 1-month post-Dose 3 as determined by N-binding antibody or NAAT.

A validated SARS-CoV-2 neutralization assay for the SARS-CoV-2 reference strain was used to obtain immunogenicity data. Immunogenicity results were reported as:

- SARS-CoV-2 50% neutralizing geometric mean titers (GMTs)
- Geometric mean ratio (GMR) of SARS-CoV-2 50% neutralizing titers
- Percentages/difference in percentages of participants who achieved seroresponse
- Geometric mean-fold rises (GMFRs) of SARS-CoV-2 50% neutralizing titers

3.3. Immunogenicity Analysis Methods

Immunogenicity analyses were based on immune responses at each time point with descriptive comparison of immune responses at 1-month post-Dose 3 compared with immune responses at 1-month post-Dose 2. Results were reported as SARS-CoV-2 50% neutralizing GMTs, the GMR of the two time points, percentages of children with seroresponse, and as the difference in percentages of children with seroresponse between the two time points, as follows.

GMTs: 2-sided 95% CIs for GMTs were obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t-distribution, then exponentiating the confidence limits. Titers below LLOQ were set to 0.5 × LLOQ.

Seroresponse: defined as achieving a ≥4-fold rise in SARS-CoV-2 neutralizing titers from baseline (before Dose 1). If the baseline measurement was below the LLOQ, the post-vaccination measure of ≥4 × LLOQ was considered seroresponse. The exact 2-sided 95% CI for percentage of participants with seroresponse was computed using the F distribution (Clopper-Pearson).

Comparison using two different groups of participants:

Comparisons are made using data at 1-month post-Dose 3 (only participants in the 3-dose set contributed data to this time point) versus all available data at 1-month post-Dose 2 (all participants in the 2-dose set and the approximately 30 participants in the 3-dose set who had blood sample collection at 1-month post-Dose 2 contributed data to this time point).

GMR: Calculated as the mean of the difference of logarithmically transformed titers between the two groups of participants at the two time points and exponentiating the mean. The associated 2-sided 95% CIs were obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

Difference in seroresponse rate: The difference in percentages of participants who achieved seroresponse and the associated 2-sided 95% CI calculated using the Miettinen and Nurminen method were provided.

Comparison within same set of participants (3-dose set with assay results at both time points):

GMR: Calculated as the mean of the difference of logarithmically transformed titers at the two time points and exponentiating the mean. The associated 2-sided 95% CIs were obtained by constructing CIs using 1-sample Student's t-distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

Difference in seroresponse rate: The 2-sided 95% CI for the difference in percentages of participants who achieved seroresponse was calculated using an adjusted Wald interval as described by Agresti and Min (2005).

Omicron Neutralization Assay

Analyses were conducted on the Omicron neutralization subset, comprised of up to approximately 30 participants in the 3-dose set (as defined above) who had blood sample collection at both 1-month post-Dose 2 and 1-month post-Dose 3. Analyses were conducted for participants either without, or with or without, evidence of prior SARS-CoV-2 infection up to 1-month post-Dose 3 as determined by N-binding antibody or NAAT results.

A fluorescent focus reduction neutralization test (FFRNT)i,ii was used to determine SARS-CoV-2 serum neutralizing titers at 1-month post-Dose 2 and 1-month post-Dose 3. The FFRNT is a non-validated assay similar to the 50% plaque-reduction neutralization test (PRNT) assay which has been used to generate confirmatory data against the reference strain and other variants.iii,iv The FFRNT assay has higher throughput and correlates well with the PRNT assay. All samples were tested at the same time to ensure comparability of results.

Briefly, 50% FFRNT titers were determined against the designated wild-type reference strain which is a recombinant USA-WA1/2020 (clinical strain isolated in January 2020), and against the B.1.1.529 Omicron variant which is a recombinant virus with the Omicron variant full spike gene on the genetic background of USA-WA1/2020. FFRNT GMTs were obtained and the GMR was calculated as described above for

'comparison within same set of participants' to compare the variant strain with the reference strain at each time point.

3.4. Results

Table 1. Immunogenicity populations

	3-Dose Set				**2-Dose Set**
	Dose 2 Evaluable		Dose 3 Evaluable		Dose 2 Evaluable
Received BNT162b2 10-µg Dose 1 and received Dose 2 within pre-defined window	X		X		X
Had 1-month post-Dose 2 assay result from blood sample collected within pre-defined window (28-42 days) after Dose 2	X				X
Had no important protocol deviations on or prior to 1-month post-Dose 2	X		X		X
Received BNT162b2 10-µg Dose 3 within pre-defined window (ie, ≥175 days post-Dose 2)			X		
Had 1-month post-Dose 3 assay result from blood sample collected within pre-defined window (28-42 days) after Dose 3			X		
Had no important protocol deviations on or prior to 1-month post-Dose 3			X		

Within the immunogenicity set, some participants had blood draws available for immunogenicity testing at either the 1-month post-Dose 2 or 1-month post-Dose 3 time points, but not necessarily both. The use of the 2-dose set, and 3-dose set was to ensure adequate blood draws and analyzed samples to determine both post-Dose 2 and post-Dose 3 immune responses.

The Dose 3 evaluable immunogenicity population included 115 children 5 to <12 years of age who received a booster (third) dose of BNT162b2 10-µg, of whom 67 participants were without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 3 (Table 2). The number of participants without prior infection was impacted by the Omicron wave that overlapped with Dose 3 administration. Exclusions from the Dose 3 evaluable population applied to a total of 8 participants (4.2%), most due to lack of a valid and determinate assay immunogenicity result after Dose 3 (4.9%).

Table 2. Immunogenicity Populations – Phase 2/3 – Immunogenicity Set – 5 to <12 Years of Age

	Vaccine Group (as Randomized)		
	BNT162b2 (10 µg)		
	3-Dose Set n[a] (%)	2-Dose Set n[a] (%)	Total n[a] (%)
Randomized[b]	123 (100.0)	67 (100.0)	190 (100.0)
Dose 2 all-available immunogenicity population	30 (24.4)	67 (100.0)	97 (51.1)
Participants excluded from Dose 2 all-available immunogenicity population	93 (75.6)	0	93 (48.9)
Reason for exclusion			
Did not have at least 1 valid and determinate immunogenicity result after Dose 2 from the blood sample collected at 1 month after Dose 2 visit	93 (75.6)	0	93 (48.9)
Dose 3 all-available immunogenicity population	118 (95.9)		118 (62.1)
Participants excluded from Dose 3 all-available immunogenicity population	5 (4.1)		5 (2.6)
Reason for exclusion			
Did not have at least 1 valid and determinate immunogenicity result after Dose 3	5 (4.1)		5 (2.6)
Dose 2 evaluable immunogenicity population	30 (24.4)	67 (100.0)	97 (51.1)
Without evidence of infection up to 1 month after Dose 2[c]	29 (23.6)	67 (100.0)	96 (50.5)
Participants excluded from Dose 2 evaluable immunogenicity population (2-dose)	93 (75.6)	0	93 (48.9)
Reason for exclusion[d]			
Did not receive Dose 2 within 19-42 days after Dose 1	2 (1.6)	0	2 (1.1)
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 2	93 (75.6)	0	93 (48.9)
Did not have blood draw at 1-month post–Dose 2 visit	91 (74.0)	0	91 (47.9)
Had blood draw within the window but no valid and determinate immunogenicity result obtained in laboratory	2 (1.6)	0	2 (1.1)
Dose 3 evaluable immunogenicity population	115 (93.5)		115 (60.5)
Without evidence of infection up to 1 month after Dose 3[e]	67 (54.5)		67 (35.3)
Participants excluded from Dose 3 evaluable immunogenicity population (3-dose)	8 (6.5)		8 (4.2)
Reason for exclusion[d]			
Did not receive Dose 2 within 19-42 days after Dose 1	2 (1.6)		2 (1.1)
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 3	6 (4.9)		6 (3.2)
Did not have blood draw at 1-month post–Dose 3 visit	1 (0.8)		1 (0.5)
1-month post–Dose 3 blood draw outside of window (28-42 days after Dose 3)	1 (0.8)		1 (0.5)
Had blood draw within the window but no valid and determinate immunogenicity result obtained in laboratory	4 (3.3)		4 (2.1)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: 3-Dose immunogenicity set included the first 130 participants received Dose 3 and completed 1 month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1 month post–Dose 2. 7 Participants that received age appropriate dose of BNT162b2 30 µg were excluded from further analysis.
2-Dose immunogenicity set included extra 67 participants randomly selected from previous Dose-2 evaluable immunogenicity population and without evidence of infection up to 1-month post–Dose 2 subset used for 2-dose immunobridging analysis.
a. n = Number of participants with the specified characteristic, or the total sample.
b. These values are the denominators for the percentage calculations.
c. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19.
d. Participants may have been excluded for more than 1 reason.
e. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
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Vaccine Administration and Timing

In the 3-dose set, most participants (94.6%) received Dose 3 of BNT162b2 10-µg (Table 3). Within this set, 7 participants (5.4%) who were 5 to <12 years of age at the time of study enrollment turned 12 years of age during the study during or after the BNT162b2 10-µg two-dose primary series vaccination period, then received BNT162b2 Dose 3 at the age-appropriate dose level of 30-µg. These participants were excluded from all further analyses reported herein, which were intended to evaluate a booster (third) dose of BNT162b2 10-µg only.

All participants who received Dose 3 of BNT162b2 10-µg got the booster dose ≥7 months after Dose 2, most commonly between 8 and 9 months post-Dose 2 (69.9%). The total range for timing of Dose 3 administration after Dose 2 was within 7 to 9 months.

Table 3. Vaccine as Administered – Phase 2/3 – 3-Dose Immunogenicity Set – 5 to <12 Years of Age

Vaccine (as Administered)	Vaccine Group (as Administered)
	BNT162b2 (N[a]=130) n[b] (%)
Dose 3	
BNT162b2 (10 µg)	123 (94.6)
BNT162b2 (30 µg)[c]	7 (5.4)

Note: 3-Dose immunogenicity set included the first 130 participants received Dose 3 and completed 1 month post-Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1 month post-Dose 2.
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. Participants who turned 12 years of age received the age appropriate dose of BNT162b2 30 µg and were excluded from further analysis.
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Demographics

Demographics of the Dose 3 evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 3 of BNT162b2 10-µg), which was comprised of 67 participants, are included in Table 4.

In total, most participants in this population were White (74.6%), with 6.0% Black or African American participants, 6.0% Asian participants, and 13.4% multiracial participants. There were 13.4% Hispanic/Latino participants. The median age was 8.0 years and 52.2% of participants were male. There were 4.5% of participants reported as obese, and 25.4% with comorbidities at baseline and/or obesity.

In the Dose 3 evaluable immunogenicity population (regardless of evidence of prior infection), 5/115 participants (4.3%) were baseline positive for evidence of prior SARS-CoV-2 infection.

Table 4. Demographic Characteristics – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 to <12 Years of Age – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)				
	BNT162b2 (10 µg)				
	3-Dose Set				2-Dose Set
	Dose 2 Evaluable (N[a]=29) n[b] (%)	Dose 3 Evaluable (N[a]=67) n[b] (%)	Dose 2 or Dose 3 Evaluable (N[a]=79) n[b] (%)	Dose 2 and Dose 3 Evaluable (N[a]=17) n[b] (%)	Dose 2 Evaluable (N[a]=67) n[b] (%)
Sex					
Male	15 (51.7)	35 (52.2)	41 (51.9)	9 (52.9)	39 (58.2)
Female	14 (48.3)	32 (47.8)	38 (48.1)	8 (47.1)	28 (41.8)
Race					
White	22 (75.9)	50 (74.6)	60 (75.9)	12 (70.6)	49 (73.1)
Black or African American	2 (6.9)	4 (6.0)	4 (5.1)	2 (11.8)	8 (11.9)
Asian	2 (6.9)	4 (6.0)	4 (5.1)	2 (11.8)	6 (9.0)
Multiracial	2 (6.9)	9 (13.4)	10 (12.7)	1 (5.9)	4 (6.0)
Not reported	1 (3.4)	0	1 (1.3)	0	0
Ethnicity					
Hispanic/Latino	5 (17.2)	9 (13.4)	14 (17.7)	0	8 (11.9)
Non-Hispanic/non-Latino	22 (75.9)	57 (85.1)	63 (79.7)	16 (94.1)	59 (88.1)
Not reported	2 (6.9)	1 (1.5)	2 (2.5)	1 (5.9)	0
Country					
Finland	0	0	0	0	7 (10.4)
Poland	0	0	0	0	6 (9.0)
Spain	0	0	0	0	7 (10.4)
USA	29 (100.0)	67 (100.0)	79 (100.0)	17 (100.0)	47 (70.1)
Age at Dose 1 vaccination (years)					
Mean (SD)	7.9 (1.48)	8.0 (1.65)	7.9 (1.64)	8.1 (1.41)	8.3 (1.90)
Median	8.0	8.0	8.0	8.0	9.0
Min, max	(5, 11)	(5, 11)	(5, 11)	(5, 11)	(5, 11)
Obese[c]					
Yes	2 (6.9)	3 (4.5)	5 (6.3)	0	4 (6.0)
No	27 (93.1)	64 (95.5)	74 (93.7)	17 (100.0)	63 (94.0)
Comorbidities[d]					
Yes	6 (20.7)	17 (25.4)	19 (24.1)	4 (23.5)	20 (29.9)
No	23 (79.3)	50 (74.6)	60 (75.9)	13 (76.5)	47 (70.1)

Abbreviations: CDC = Centers for Disease Control and Prevention; MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: 3-Dose immunogenicity set included the first 130 participants received Dose 3 and completed 1 month post–Dose 3 visit prior to March 15, 2022.
Among those, 30 had blood sample collection at 1 month post–Dose 2.
2-Dose immunogenicity set included extra 67 participants randomly selected from previous Dose-2 evaluable immunogenicity population and without
evidence of infection up to 1-month post–Dose 2 subset used for 2-dose immunobridging analysis.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2
(for Dose-2 evaluable) or 1-month post–Dose 3 (for Dose-3 evaluable) study blood sample collection. Having no evidence of past SARS-CoV-2 infection
up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits;
a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample
collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a
negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative
NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample
collection; and no medical history of COVID-19.
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. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. 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 of the prespecified comorbidities based on MMWR Morb Mortal Wkly Rep.2020;69(32):1081-8 and/or obesity (BMI ≥95th percentile).
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (06:55) Source Data: adsl Table Generation: 03APR2022 (01:39)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File:
./nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/adsl_s005_demo_p23_eval_wout

SARS-CoV-2 Neutralizing Titers – Reference Strain

SARS-CoV-2 neutralizing titer data for Phase 2/3 participants 5 to <12 years of age who received a booster (third) dose of BNT162b2 10-µg are summarized below for the Dose 3 evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection.

Results in the Dose 3 evaluable immunogenicity population (regardless of evidence of prior infection) and the Dose 3 all-available immunogenicity population were generally similar, noting there are differences in sample sizes between the analysis sets and noting that higher titers were observed when individuals with prior evidence of infection were included in the analysis.

Analysis data include the total evaluable immunogenicity population, comprised of the combined 2-dose set (participants who completed the 1-month post-Dose 2 visit) and 3-dose set (participants who completed the 1-month post-Dose 3 visit). Additionally, data are presented for participants in the 3-dose set who had assay results at both post-Dose 2 and post-Dose 3.

Table 5. Summary of Geometric Mean Titers – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 to <12 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)								
		BNT162b2 (10 µg)								
		3-Dose Set			2-Dose Set			Total		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	1/Prevax	79	20.5	(20.5, 20.5)	67	20.5	(20.5, 20.5)	146	20.5	(20.5, 20.5)
	2/1 Month	29	1659.4	(1385.1, 1988.0)	67	1110.7	(965.3, 1278.1)	96	1253.9	(1116.0, 1408.9)
	3/Prevax	67	271.0	(229.1, 320.6)				67	271.0	(229.1, 320.6)
	3/1 Month	67	2720.9	(2280.1, 3247.0)				67	2720.9	(2280.1, 3247.0)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: 3-Dose immunogenicity set included the first 130 participants received Dose 3 and completed 1 month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1 month post–Dose 2.
2-Dose immunogenicity set included extra 67 participants randomly selected from previous Dose-2 evaluable immunogenicity population and without evidence of infection up to 1-month post–Dose 2 subset used for 2-dose immunobridging analysis.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 timepoint) or 1-month post–Dose 3 (for pre–Dose 3 and 1-month post–Dose 3 timepoints) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
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Geometric Mean Titers (GMTs) – Reference Strain

Among the total set of participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection (across the combined 2-dose set and 3-dose set), there was a substantial increase in SARS-CoV-2 50% neutralizing titers against the reference strain of SARS-CoV-2 after Dose 3 compared to before Dose 3 (Figure 1 and Figure 2). The observed GMTs increased from pre-vaccination of 20.5 (n=146) to 1253.9 at 1-month post-Dose 2 (n=96), had waned to 271.0 by the time of booster vaccination prior to receipt of Dose 3 (n=67), and were substantially boosted to 2720.9 at 1-month post-Dose 3 (n=67).

Note that the total of available titers across the combined 3-dose and 2-dose sets in Table 5 was the basis of further analyses of GMFR, GMR, and differences in seroresponse rates.

Among 17 participants without prior evidence of infection in the 3-dose set with assay results at both 1-month post-Dose 2 and at 1-month post-Dose 3, the GMTs at 1-month post-Dose 2, pre-Dose 3, and 1-month post-Dose 3 were 1685.7, 234.9, and 2611.8, respectively (Table 6).

Table 6. Summary of Geometric Mean Titers – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – Participants with Assay Result at Both 1 Month Post–Dose 2 and 1 Month Post–Dose 3 – 5 to <12 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)		
		BNT162b2 (10 µg)		
		3-Dose Set		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c]	(95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	1/Prevax	17	20.5	(20.5, 20.5)
	2/1 Month	17	1685.7	(1402.8, 2025.5)
	3/Prevax	17	234.9	(185.9, 296.9)
	3/1 Month	17	2611.8	(1898.9, 3592.4)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: 3-Dose immunogenicity set included the first 130 participants received Dose 3 and completed 1 month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1 month post–Dose 2.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2, Dose 3 and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 study blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
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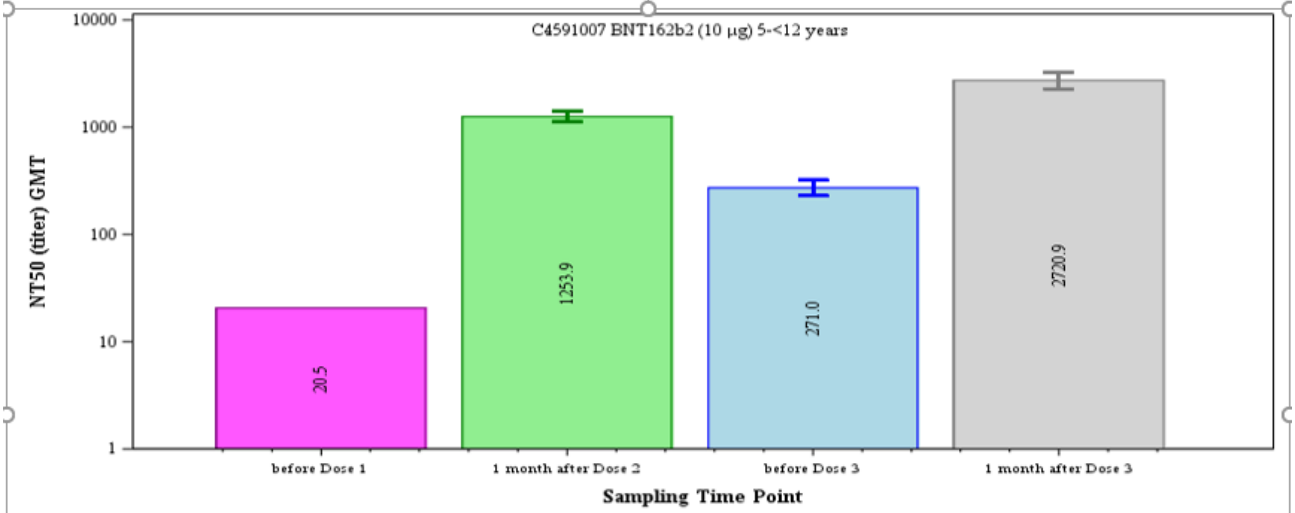
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File: ./nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/adva_s001_gm_p23_wout_evl_1md3

Figure 1. Geometric Mean Titers and 95% CIs: SARS-CoV-2 Neutralization Assay – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 to <12 Years of Age – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Number within each bar denotes geometric mean.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 timepoint) or 1-month post–Dose 3 (for pre–Dose 3 and 1-month post–Dose 3 timepoints) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
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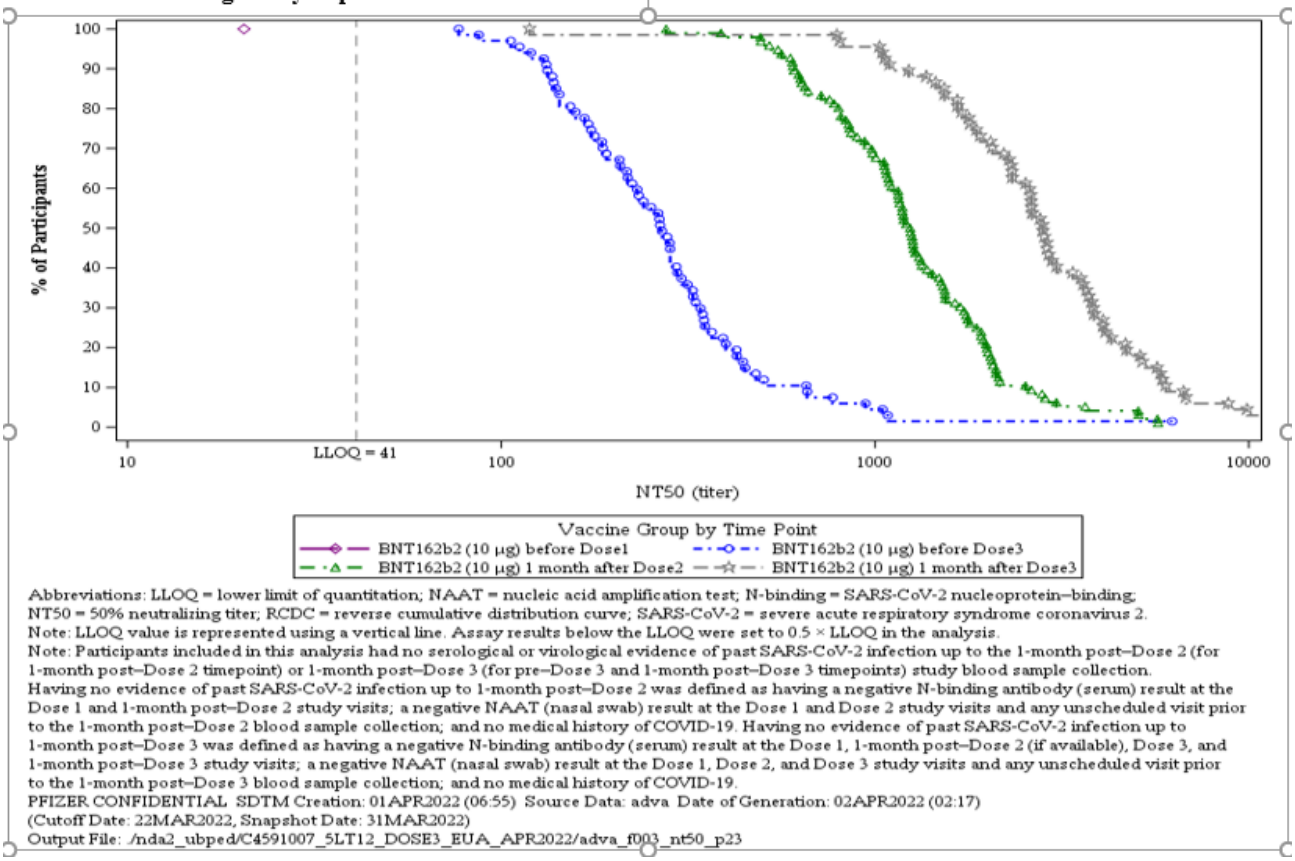
Output File: /nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/adva_f002_nt50_p23_evl_wout

Figure 2. Reverse Cumulative Distribution Curves, SARS-CoV-2 Neutralization Assay - NT50 – Without Evidence of Infection –Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Evaluable Immunogenicity Population



Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; RCDC = reverse cumulative distribution curve; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: LLOQ value is represented using a vertical line. Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 timepoint) or 1-month post–Dose 3 (for pre–Dose 3 and 1-month post–Dose 3 timepoints) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
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Output File: /nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/adva_f003_nt50_p23

Geometric Mean Fold-Rise (GMFR) in Titers – Reference Strain

Among 67 participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection, the GMFR of SARS-CoV-2 50% serum neutralizing titers from Dose 3 to 1 month after Dose 3 was 10.0 (2-sided 95% CI: 8.1, 12.4).

In the evaluable immunogenicity population (regardless of evidence of prior infection; n=112), the GMFR from Dose 3 to 1 month after Dose 3 was 6.2 (2-sided 95% CI: 5.0, 7.6); and in the all-available immunogenicity population (n=115) the GMFR from Dose 3 to 1 month after Dose 3 was 6.2 (2-sided 95% CI: 5.1, 7.7). In these populations, the inclusion of participants with prior infection with SARS-CoV-2, who typically have a higher pre-Dose 3 titer, appears to slightly blunt the overall fold-rise in titers after vaccination, noting that the observed GMTs were substantially elevated at 1-month post-Dose 3 regardless of prior SARS-CoV-2 status.

Geometric Mean Ratio (GMR) of Neutralizing Titers – Reference Strain

The ratio of neutralizing titers available at 1-month post-Dose 3 versus titers available at 1-month post-Dose 2 for the evaluable immunogenicity population without evidence of prior infection were summarized based on:

1-month post-Dose 3 group results: n=67 who received a booster (third) dose of BNT162b2 10-µg and were without evidence of SARS-CoV-2 infection up to 1-month post-Dose 3.

1-month post-Dose 2 group results: n=96 regardless of receiving a booster or not and were without evidence of infection up to 1-month post-Dose 2.

The GMR comparing 1-month post-Dose 3 to 1-month post-Dose 2 was 2.17 (2-sided 95% CI: 1.76, 2.68) (Table 7).

Among 17 participants without prior evidence of SARS-CoV-2 infection in the 3-dose set with assay results at both 1-month post-Dose 2 and at 1-month post-Dose 3, the GMR was 1.55 (2-sided 95% CI: 1.11, 2.17) (Table 8).

Table 7. Summary of Geometric Mean Ratios – NT50 – Comparison of 1-Month After Dose 3 With 1-Month After Dose 2 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 to <12 Years of Age – Evaluable Immunogenicity Population

		Sampling Time Point[a]							
		1-Month Post–Dose 3 (for 1MPD3 Group)			1-Month Post–Dose 2 (for 1MPD2 Group)			1-Month Post–Dose 3 (for 1MPD3 Group)/ 1-Month Post–Dose 2 (for 1MPD2 Group)	
Assay	Vaccine Group (as Randomized)	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	GMR[d]	(95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	BNT162b2 (10 µg)	67	2720.9	(2280.1, 3247.0)	96	1253.9	(1116.0, 1408.9)	2.17	(1.76, 2.68)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: The 1-month post–Dose 3 (1MPD3) group includes participants in the 3-dose immunogenicity set who had assay results at 1-month post–Dose 3 and the 1-month post–Dose 2 (1MPD2) group includes participants in the 2-dose or 3-dose immunogenicity set who had assay results at 1-month post–Dose 2.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1 month post–Dose 2 timepoint) or 1-month post–Dose 3 (for 1-month post–Dose 3 timepoint) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers ([1MPD3 Group at 1-Month Post–Dose 3 timepoint] - [1MPD2 Group at 1-Month Post–Dose 2 timepoint]) and the corresponding CI (based on the Student t distribution).
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Table 8. Summary of Geometric Mean Ratios – NT50 – Comparison of 1-Month After Dose 3 With 1-Month After Dose 2 – Participants Without Evidence of Infection – Phase 2/3 Immunogenicity Set – Participants with Assay Result at Both 1 Month Post–Dose 2 and 1 Month Post–Dose 3 – 5 to <12 Years of Age – Evaluable Immunogenicity Population

			Sampling Time Point[a]		
			1-Month Post–Dose 3	1-Month Post–Dose 2	1-Month Post–Dose 3/ 1-Month Post–Dose 2
Assay	Vaccine Group (as Randomized)	n[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	BNT162b2 (10 µg)	17	2611.8 (1898.9, 3592.4)	1685.7 (1402.8, 2025.5)	1.55 (1.11, 2.17)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2, Dose 3 and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the
Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 study blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at both sampling time points.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (1-month post–Dose 3 – 1-month post–Dose 2) and the corresponding CI (based on the 1-sample Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (06:55) Source Data: adva Table Generation: 02APR2022 (21:58)
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Seroresponse Rate – Reference Strain

Among the total set of participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection (across the combined 2-dose set and 3-dose set), the observed proportion of participants who achieved seroresponse in SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2 (n=96) was 100.0% (Table 9). The observed seroresponse rate had waned to 77.6% by the time of booster vaccination prior to receipt of Dose 3 (n=67) and was then substantially increased at 1-month post-Dose 3 (n=67) to 98.5%.

Among 17 participants without prior evidence of SARS-CoV-2 infection in the 3-dose set with assay results at both 1-month post-Dose 2 and at 1-month post-Dose 3, the observed proportions of participants with seroresponse at 1-month post-Dose 2, pre-Dose 3, and 1-month post-Dose 3 were 100.0%, 70.6%, and 100.0%, respectively (Table 10).

Table 9. Number (%) of Participants With Seroresponse – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 to <12 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)								
		BNT162b2 (10 µg)								
		3-Dose Set			2-Dose Set			Total		
Assay	Dose/ Sampling Time Point[a]	N[b]	n[c]	% (95% CI[d])	N[b]	n[c]	% (95% CI[d])	N[b]	n[c]	% (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	29	29	100.0 (88.1, 100.0)	67	67	100.0 (94.6, 100.0)	96	96	100.0 (96.2, 100.0)
	3/Prevax	67	52	77.6 (65.8, 86.9)				67	52	77.6 (65.8, 86.9)
	3/1 Month	67	66	98.5 (92.0, 100.0)				67	66	98.5 (92.0, 100.0)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
Note: 3-Dose immunogenicity set included the first 130 participants received Dose 3 and completed 1 month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1 month post–Dose 2. 2-Dose immunogenicity set included extra 67 participants randomly selected from previous Dose-2 evaluable immunogenicity population and without evidence of infection up to 1-month post–Dose 2 subset used for 2-dose immunobridging analysis.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 timepoint) or 1-month post–Dose 3 (for pre–Dose 3 and 1-month post–Dose 3 timepoints) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay both at baseline (before Dose 1) and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
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(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File: ./nda2 ubped/C4591007 5LT12 DOSE3 EUA APR2022/adva s003 4fr p23 evl wout

Table 10. Number (%) of Participants with Seroresponse – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – Participants With Assay Result at Both 1 Month Post–Dose 2 and 1 Month Post–Dose 3 – 5 to <12 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)		
		BNT162b2 (10 µg)		
		3-Dose Set		
Assay	Dose/ Sampling Time Point[a]	N[b]	n[c]	% (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	17	17	100.0 (80.5, 100.0)
	3/Prevax	17	12	70.6 (44.0, 89.7)
	3/1 Month	17	17	100.0 (80.5, 100.0)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
Note: 3-Dose immunogenicity set included the first 130 participants received Dose 3 and completed 1 month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1 month post–Dose 2.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2, Dose 3 and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 study blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay both at baseline (before Dose 1) and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (06:55) Source Data: adva Table Generation: 02APR2022 (02:26)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File: ./nda2 ubped/C4591007 5LT12 DOSE3 EUA APR2022/adva s003 4fr p23 evl wout d3

Difference in Seroresponse Rate – Reference Strain

The difference in proportions of participants achieving seroresponse with titers available at 1-month post-Dose 3 versus titers available at the 1-month post-Dose 2 for the evaluable immunogenicity population without evidence of prior infection were summarized based on:

1-month post-Dose 3 group results: n=67 who received a booster (third) dose of BNT162b2 10-µg and were without evidence of SARS-CoV-2 infection up to 1-month post-Dose 3.

1-month post-Dose 2 group results: n=96 regardless of receiving a booster or not and were without evidence of infection up to 1-month post-Dose 2.

Seroresponse was achieved by 98.5% of participants 1-month post-Dose 3 and by 100.0% of participants at 1-month post-Dose 2. The difference in seroresponse rates (1 month after Dose 3 – 1 month after Dose 2) was -1.5% (2-sided 95% CI: -8.0%, 2.4%) (Table 11).

Among 17 participants in the 3-dose set with assay results at both 1-month post-Dose 2 and at 1-month post-Dose 3, the difference in seroresponse rates was 0.0% (2-sided 95% CI: -10.3%, 10.3%) (Table 12).

Table 11. Difference in Percentages of Participants with Seroresponse – Comparison of 1-Month After Dose 3 With 1-Month After Dose 2 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – Phase 2/3 – 5 to <12 Years of Age – Evaluable Immunogenicity Population

		Sampling Time Point							
		1-Month Post–Dose 3 (for 1MPD3 Group)			1-Month Post–Dose 2 (for 1MPD2 Group)			Difference	
Assay	Vaccine Group (as Randomized)	N[a]	n[b]	% (95% CI[c])	N[a]	n[b]	% (95% CI[c])	%[d]	(95% CI[e])
SARS-CoV-2 neutralization assay - NT50 (titer)	BNT162b2 (10 µg)	67	66	98.5 (92.0, 100.0)	96	96	100.0 (96.2, 100.0)	-1.5	(-8.0, 2.4)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
Note: The 1-month post–Dose 3 (1MPD3) group includes participants in the 3-dose immunogenicity set who had assay results at 1-month post–Dose 3 and the 1-month post–Dose 2 (1MPD2) group includes participants in the 2-dose or 3-dose immunogenicity set who had assay results at 1-month post–Dose 2.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1 month post–Dose 2 timepoint) or 1-month post–Dose 3 (for 1-month post–Dose 3 timepoint) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. N = number of participants with valid and determinate assay results for the specified assay both at baseline (before Dose 1) and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage ([1MPD3 Group at 1-Month Post–Dose 3 timepoint] – [1MPD2 Group at 1-Month Post–Dose 2 timepoint]).
e. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (06:55) Source Data: adva Table Generation: 02APR2022 (22:30)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File: ./nda2 ubped/C4591007 5LT12 DOSE3 EUA APR2022/adva s005 diff1 p23 evl wout

Table 12. Difference in Percentages of Participants With Seroresponse – Comparison of 1-Month After Dose 3 With 1-Month After Dose 2 – Participants Without Evidence of Infection – Phase 2/3 – 5 to <12 Years of Age – Immunogenicity Set – Participants With Assay Result at Both 1 Month Post–Dose 2 and 1 Month Post–Dose 3 – Evaluable Immunogenicity Population

		Sampling Time Point						
		1-Month Post–Dose 3			1-Month Post–Dose 2		Difference	
Assay	Vaccine Group (as Randomized)	N[a]	n[b]	% (95% CI[c])	n[b]	% (95% CI[c])	%[d]	(95% CI[e])
SARS-CoV-2 neutralization assay - NT50 (titer)	BNT162b2 (10 µg)	17	17	100.0 (80.5, 100.0)	17	100.0 (80.5, 100.0)	0.0	(-10.3, 10.3)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2, Dose 3 and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 study blood sample collection; and no medical history of COVID-19.
a. N = number of participants with valid and determinate assay results for the specified assay at baseline (before Dose 1) and at both sampling time points. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage ([1-Month Post–Dose 3] – [1-Month Post–Dose 2]).
e. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (06:55) Source Data: adva Table Generation: 02APR2022 (22:30)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File: ./nda2 ubped/C4591007 5LT12 DOSE3 EUA APR2022/adva s005 diff1 p23 evl wo1md3

SARS-CoV-2 Neutralizing Titers – Omicron Variant

FFRNT data for Phase 2/3 participants 5 to <12 years of age who received a booster (third) dose of BNT162b2 10-µg are summarized below for the evaluable immunogenicity population of participants without prior evidence of SARS-CoV-2 infection. This included n=29 with assay results available at 1-

month post-Dose 2 and without evidence of infection up to 1 month after Dose 2, and n=17 with assay results and without evidence of infection up to 1-month post-Dose 3.

Results in the evaluable immunogenicity population (regardless of evidence of prior infection) and the all-available immunogenicity population were generally similar, noting that higher titers were observed when individuals with prior evidence of infection were included in the analysis.

Geometric Mean Titers (GMTs)

The neutralizing GMTs against both the Omicron variant and reference strain were substantially increased after booster vaccination compared with after the two-dose primary series (Table 13). At 1-month post-Dose 2, the observed neutralizing GMTs for the Omicron variant and reference strain were 27.6 and 323.8, respectively. At 1-month post-Dose 3, the observed neutralizing GMTs for the Omicron variant and reference strain were 614.4 and 1702.8, respectively.

For the Omicron variant, neutralizing titers after booster vaccination (1-month post-Dose 3) increased 22-fold over those after the two-dose primary series (1-month post-Dose 2). For the reference strain, the increase after the booster relative to the primary series was 5-fold.

Geometric Mean Ratios (GMRs)

The GMR of neutralizing titers against Omicron versus the reference strain was increased after booster vaccination (1-month post-Dose 3) relative to after the two-dose primary series (1-month post-Dose 2) (Table 14) as follows.

1-month post-Dose 2: GMR of titers against the Omicron variant vs reference strain was 0.09 (2-sided 95% CI: 0.07, 0.10).

1-month post-Dose 3: GMR of titers against the Omicron variant vs reference strain was 0.36 (2-sided 95% CI: 0.28, 0.47).

The GMRs show a fold-rise from 1-month post-Dose 2 to 1-month post-Dose 3 that was 4-times higher for the Omicron titers than for the reference strain titers obtained in the FFRNT assay.

Table 13. Summary of Geometric Mean Titers – Omicron-Neutralization Subset – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 to <12 Years of Age – Evaluable Immunogenicity Population

Assay	Dose/ Sampling Time Point[a]	Vaccine Group (as Randomized) BNT162b2 (10 µg) n[b]	GMT[c] (95% CI[c])
SARS-COV-2 FFRNT-strain B.1.1.529 (Omicron) -NT50 (titer)	2/1 Month	29	27.6 (22.1, 34.5)
	3/1 Month	17	614.4 (410.7, 919.2)
SARS-CoV-2 FFRNT- reference strain - NT50 (titer)	2/1 Month	29	323.8 (267.5, 392.1)
	3/1 Month	17	1702.8 (1282.6, 2260.7)

Abbreviations: FFRNT=fluorescence focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation;
NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2
(for 1-month post–Dose 2 timepoint) or 1-month post–Dose 3 (for 1-month post–Dose 3 timepoint) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month
post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month
post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month
post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and
1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assays at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (06:55) Source Data: adva Table Generation: 02APR2022 (02:25)
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Table 14. Summary of Geometric Mean Ratios – Omicron-Neutralization Subset – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 to <12 Years of Age – Evaluable Immunogenicity Population

Assay	Dose/ Sampling Time Point[a]	Vaccine Group (as Randomized) BNT162b2 (10 µg) n[b]	GMR[c] (95% CI[c])
SARS-COV-2 FFRNT-strain B.1.1.529 (Omicron) - NT50 (titer) to SARS-CoV-2 FFRNT - reference strain - NT50 (titer)	2/1 Month	29	0.09 (0.07, 0.10)
	3/1 Month	17	0.36 (0.28, 0.47)

Abbreviations: FFRNT=Fluorescence focus reduction neutralization test; GMR = geometric mean ratio; LLOQ = lower limit of quantitation;
NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2
(for 1 month post–Dose 2 timepoint) or 1-month post–Dose 3 (for 1-month post–Dose 3 timepoint) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month
post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month
post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month
post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month
post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the
1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for both the specified assays at the given dose/sampling time point.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean differences in the logarithms of the assays and the corresponding CIs (based on the 1-sample Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (06:55) Source Data: adva Table Generation: 02APR2022 (02:30)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File:
./nda2 ubped/C4591007 5LT12 DOSE3 EUA APR2022/adva s004 gmr1 om p23 evl wout

3.5. Immunogenicity Discussion

Study C4591007 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 study including healthy children from 6 months to <12 years of age. The dose selection of Phase 1 show that the suitable dose of Comirnaty for 5 to <12 years is 10-µg. In Phase 2/3 the participants randomized 2:1 to receive vaccine or placebo, and conducted at sites in the US, Finland, Poland, and Spain. The primary series of BNT162b2 was initially planned as a two-dose series; however, based on emerging clinical and real-world data, the protocol was amended to add a third dose. The participants could be unblinded to treatment assignment at 6 months after Dose 2.

The protocol specified timing of booster vaccination for participants 5 to <12 years of age was ≥6 months after Dose 2); therefore, booster (third) doses have been administered to participants in this age group in an open-label manner. Participants in the study will continue to be followed in an open-label observational manner until the end of the study which is acceptable.

The basis of demonstrating BNT162b2 effectiveness in children is immune response data which is acceptable. Immunogenicity data include SARS-CoV-2 neutralizing titers against the wild-type strain and Omicron variant after a booster (third) dose of BNT162b2 10-µg, up to 1-month post-Dose 3.

The immunogenicity set was comprised of:

3-Dose set: included up to 130 participants who received Dose 3 and completed the 1-month post-Dose 3 visit prior to 15 March 2022. Within this set, up to 30 participants also had blood sample collection at 1-month post-Dose 2; sera from these participants were also analyzed for Omicron neutralization. This 3-dose set came exclusively from US.

2-Dose set: included up to 70 additional participants randomly selected from the previously analyzed Dose 2 evaluable immunogenicity population who were without evidence of prior infection up to 1-month post-Dose 2 (ie, included in the two-dose immunobridging analysis). These additional participants were included to ensure sufficient post-Dose 2 data for analyses. About 30 % of 2-dose set came from EU and 70 % from US.

Immunogenicity results were reported as in previous Comirnaty authorization studies:

- SARS-CoV-2 50% neutralizing geometric mean titers (GMTs)
- Geometric mean ratio (GMR) of SARS-CoV-2 50% neutralizing titers
- Percentages/difference in percentages of participants who achieved seroresponse
- Geometric mean-fold rises (GMFRs) of SARS-CoV-2 50% neutralizing titers

A validated SARS-CoV-2 neutralization assay for the SARS-CoV-2 reference strain was used, but for Omicron variant, unvalidated assay FFRNT was used, which may affect the robustness of the data obtained. The MAH answered that non-validated assays have been used also earlier.

Analyses were conducted for participants either without, or with or without, evidence of prior SARS-CoV-2 infection up to 1-month post-Dose 2 or 1-month post-Dose 3 as determined by N-binding antibody or NAAT. As the pandemic has been evolved, the study population without evidence of previous SARS-COV-2 infection has been decreased. In addition, there was not many blood samples available from post-dose 1 and 2. This resulted in reduced sample size. The biological variability to respond to vaccine is wide especially after booster dose, therefore it is needed multiple observations to ensure the representability of the results for general population. Therefore at least 50 subjects per group is desirable. Currently too few observations in post-dose 2 demonstrate the biological variability of immune response in 3-dose set (US N=29) compared to the 2 dose-set (US+EU N=67). The GMT values which are expected to be very similar do not have even overlapping CI, see below excerpt from table 4.

Immunogenicity set	**N**	**Post-dose 2 (GMT 95% CI)**	**Pre dose 3**	**Post dose 3**
2-dose set (US+EU)	29	*1111 (965; 1278)*		
3-dose set (US)	67	*1659 (1385; 1988)*	271 (229; 321)	2721 (2280; 3247)
Total	96	1254 (1116; 1409)		

To avoid confusion, we recommend not to present GMT separately for 2 and 3 dose sets. The MAH agreed with simplified presentation of the results.

There were only 17 subjects, who had no signs of SARS-COV-2 during entire study period, had received all 3 vaccinations in correct time frame and had all blood samples available after each vaccination. This is

very limited cohort. These subjects were tested to evaluate neutralizing antibodies against Wuhan strain using validated neutralization and also non-validated FFRNT assay for both Wuhan and Omicron strains.

A validated SARS-CoV-2 neutralization assay and unvalidated FFRNT assay show antibody rise 2 vs 3 doses for Wuhan strain, but the values differ a lot. The observed differences in GMT ratios can not be attributable only for the small sample size and high variability of immunological responses, but is a sign that the assays do not have a good agreement, see below excerpts from table 8 and 13.

Wuhan neutralization	**N**	**Post-dose 2 (GMT 95% CI)**	**N**	**Post dose 3**	**GMT Ratio 3/2**
Validated neutralization assay	17	1686 (1403; 2026)	17	2612 (1899; 3592)	1.5
FFRNT	29	324 (268; 392)	17	1703 (1283; 2261)	5.3

Due to the limited sample size and unvalidated FFRNT assay we recommend removing the text in SmPC describing 3rd dose impact on Omicron variant neutralization. The MAH still will add a summary statement to the SMPC, which can be agreed with.

The booster dose induced neutralizing titres against the omicron BA.1 strain which were approx. 1.9-fold higher than those observed after primary vaccination against the index strain (GMT 614 versus 323). As the BA.1 omicron lineage has been replaced by BA.2.12.1, BA.4 and BA.5 lineages, it would be of interest to confirm that the immunogenicity of the booster dose as documented by titres against the no longer circulating BA.1 remain valid/true for the currently circulating BA.2.12.1, BA.4 and BA.5 lineages. This can be done by using the children sera from the immunobridging trial to perform in vitro neutralization assays against omicron BA.2.12.1, BA.4 and BA.5 lineages to allow a comparison between omicron subspecies.

The MAH was therefore asked to provide a plan and timelines for the availability of data regarding other omicron VOCs i.e. BA.2, BA.4 and BA.5. The MAH answered that Neutralization of Omicron sublineages, including BA.2, BA.2.12.1, and BA.4/BA.5 has been evaluated in sera from the phase 1 participants 23 to 74 years of age in the C4591001 pivotal study. BNT162b2 post-Dose 3 immune sera neutralized USA-WA1/2020, Omicron BA.1-, BA.2-, BA.2.12.1-, BA.3-, BA.4/5-, and XD-spike SARS-CoV-2s with geometric mean titers (GMTs) of 1335, 393, 298, 315, 216, 103, and 301, respectively; thus, BA.4/5 SARS-CoV-2 spike variant showed the highest propensity to evade vaccine neutralization compared to the original Omicron variants BA.1. As neutralization trends against the reference strain (USA-WA-1/2020) and Omicron BA.1 have been consistent across age groups (adults and 5-11-year olds), we would anticipate similar trends against the Omicron sublineages as shown in Kuhade et al.

Testing is not planned in the 5-11-year-old age group as data in this age group have been consistent with what has been observed in the adult population.

Generally, all the immunological results showed that higher neutralising titres are obtained after the third dose compared to the second dose of Comirnaty 10 µg among children ages 5 to below 12. This is expected result as demonstrated earlier for adults with Comirnaty 30 µg. Also, the neutralising titres had declined before the third dose compared to 1 month after dose 2, as can be expected. The seroresponse rate was almost 100% after 3rd dose. There was one non-responder observed with very low GMT values after 3 doses. This was unexpected, but do not negatively affect the booster authorization.

The main immune responses were the following:

In an evaluable immunogenicity population of 67 children 5 to <12 years of age who were without evidence of SARS-CoV-2 infection the following immunogenicity responses were observed:

GMTs at 1-month post-Dose 3 were increased (2720.9) compared with those at 1-month post-Dose 2 (1253.9) and prior to booster (Dose 3) vaccination (271.0).

The GMR for participants with available titers at 1-month post-Dose 3 compared to those with available titers at 1-month post-Dose 2 was 2.17 (2-sided 95% CI: 1.76, 2.68).

The observed proportion of participants who achieved seroresponse was high (100.0%) at 1-month post-Dose 2, waned by pre-Dose 3 (77.6%), and was increased at 1 month after Dose 3 (98.5%).

Based on the unvalidated FFRNT assay, a booster (third) dose of BNT162b2 10-µg elicited neutralizing titers against a recombinant SARS-CoV-2 Omicron variant and recombinant wild-type (reference) strain of SARS-CoV-2 in an evaluable immunogenicity population of 29 children 5 to <12 years of age who were without evidence of SARS-CoV-2 infection.

The observed 1-month post-Dose 2, neutralizing GMTs for the Omicron variant and reference strain were 27.6 and 323.8, respectively which increased at 1-month post-Dose 3 to 614.4 and 1702.8 and, respectively, representing an increase from post-two-dose primary series to post-booster vaccination of 22-fold for Omicron and 5-fold for the reference strain.

The immune response associated with a booster (third) dose of BNT162b2 10-µg administered approximately 6 months after the second dose to children 5 to <12 years of age is expected to confer protection against COVID-19 including disease caused by Omicron.

Taking into consideration the current SmPC recommendations in individuals 12 years of age and older, the MAH is invited to consider the minimum boosting interval. MAH did not change their statement, that booster should be administered after 6 months from dose 2 in this young age group and this issue is not pursued further.

4. Clinical Safety aspects

4.1. Introduction

The safety database constitutes of interim data from a phase 1/2/3 study (C4591007) including children aged 5-<12 years of age that have received a booster dose (third dose) of BNT162b 10 µg. The study was conducted at 68 sites, which included sites in Finland (11), Poland (8), Spain (10), and the US (39). The Phase 2/3 was initiated 7 June 2021, and the database lock point for this interim analysis is 22 March 2022. All Phase 2/3 participants were to be unblinded at the 6-month follow-up visit, per protocol. The booster (third) dose of BNT162b2 10-µg was to be administered at least 6 months after the second dose, after participants were to be unblinded, therefore in an open-label manner.

Reactogenicity: Local reactions, systemic events, and antipyretic/pain medication use was recorded each evening for 7 days after each dose administration using prompts from an electronic diary (e-diary). Grading scales were based on FDA guidance.

Adverse Events: AEs were collected from Dose 3 to 1 month after Dose 3 and serious AEs (SAEs) are collected from Dose 3 to 6 months after Dose 3. AEs are categorized by frequency, maximum severity, seriousness, and relationship to study intervention using system organ class (SOC) and preferred term (PT) according to MedDRA. Deaths are recorded to the end of study.

Inclusion/Exclusion criteria: Enrolled into Phase 2/3 of this study were healthy participants who were determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study in the protocol specified age groups. Eligibility permitted enrolment of participants with medical conditions such as stable Type 1 diabetes or hypothyroidism; stable and controlled HIV, HCV, or HBV infection; and past serological or microbiological evidence of prior (not active) SARS-CoV-2 infection. Participants' parent(s)/legal guardian(s) had to provide signed inform consent (and verbal or written assent from the participant if appropriate); they also had to be willing and able to comply with all scheduled visits, treatment plans, laboratory tests, lifestyle considerations, and other study procedures. Exclusions from Phase 2/3 study participation included prior receipt of a COVID-19 vaccine or medication intended to prevent COVID-19, prior or current diagnosis of MIS-C, history of severe (i.e., anaphylactic) reaction associated with any vaccine or allergy to any component of the study intervention (i.e., BNT162b2), immunodeficiency or autoimmune disease requiring therapeutic intervention (other than diabetes) and other medical conditions and/or therapeutic interventions deemed incompatible with study participation.

4.2. Methods

4.2.1. Disposition

All participants included in the safety population received Dose 1, Dose 2, and Dose 3 as illustrated in the table below. One protocol deviation was reported for one participant (0.2%) who had an important protocol deviation of incorrect vaccine allocation/assigned. This participant was randomized to placebo but received two doses of BNT162b2 10-µg and a booster (third) dose of BNT162b2 10-µg.

All participants included in the safety population received Dose 1, Dose 2, and Dose 3 (Table 15). As of the data cut-off date (22 March 2022), 77.6% of participants 5 to <12 years of age who received Dose 3 of BNT162b2 10-µg completed the visit at 1 month after Dose 3. No participants discontinued from the vaccination period or were withdrawn from the study as of the data cut-off date (22 March 2022).

Table 15. Disposition of Participants – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)
	BNT162b2 (10 µg) (N[a]=401) n[b] (%)
Received Dose 3	401 (100.0)
Completed 1-month post–Dose 3 visit (Dose 3 vaccination period)	311 (77.6)
Discontinued from Dose 3 vaccination period but continued in the study	0
Withdrawn from the study after Dose 3	0

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (10:56) Source Data: adds Table Generation: 01APR2022 (14:35)
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All participants who received Dose 3 of BNT162b2 10-µg received the booster dose ≥5 months after Dose 2, most commonly between 8- and 9-months post-Dose 2 (86.8%). The total range for timing of Dose 3 administration after Dose 2 was 5 to 9 months. Subjects that turned 12 years of age (n=24) received 30µg and where therefore excluded. The safety population analysed for Phase 2/3 participants 5 to <12 years of age who received a booster (third) dose of BNT162b2 10-µg included N=401. No participants in the safety population were HIV+. No participants were excluded from the safety population for any reason.

Table 16. Vaccine as Administered – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population

Vaccine (as Administered)	Vaccine Group (as Administered) BNT162b2 (N[a]=425) n[b] (%)
Dose 3	
BNT162b2 (10 µg)	401 (94.4)
BNT162b2 (30 µg)[c]	24 (5.6)

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. Participants who turned 12 years of age received the age appropriate dose of BNT162b2 30 µg and were excluded from further analysis.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (06:55) Source Data: adsl Table Generation: 01APR2022 (14:35)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File:
./nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/advx_s002_adm_p23_rand

Table 17. Vaccine Administration Timing – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered) BNT162b2 (10 µg) (N[a]=401) n[b] (%)
Vaccinated Dose 3	401 (100.0)
Dose 3[c]	
≥5-<6 Months	1 (0.2)
≥6-<7 Months	1 (0.2)
≥7-<8 Months	51 (12.7)
≥8-<9 Months	348 (86.8)

1. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
2. n = Number of participants with the specified characteristic.
3. Months calculated since Dose 2.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (06:55) Source Data: adsl Table Generation: 01APR2022 (14:35)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File:
./nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/advx_s002_time_p23_rand

4.2.2. Demographics

Table 18. Demographic Characteristics – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)
	BNT162b2 (10 µg) (N[a]=401) n[b] (%)
Sex	
Male	210 (52.4)
Female	191 (47.6)
Race	
White	281 (70.1)
Black or African American	29 (7.2)
American Indian or Alaska Native	8 (2.0)
Asian	31 (7.7)
Native Hawaiian or other Pacific Islander	1 (0.2)
Multiracial	46 (11.5)
Not reported	5 (1.2)
Ethnicity	
Hispanic/Latino	92 (22.9)
Non-Hispanic/non-Latino	306 (76.3)
Not reported	3 (0.7)
Country	
USA	401 (100.0)
Age at Dose 1 vaccination (years)	
Mean (SD)	7.9 (1.75)
Median	8.0
Min, max	(5, 11)
Obese[c]	
Yes	39 (9.7)
No	362 (90.3)
Baseline SARS-CoV-2 status	
Positive[d]	22 (5.5)
Negative[e]	379 (94.5)
Comorbidities[f]	
Yes	119 (29.7)
No	282 (70.3)

	Vaccine Group (as Administered)
	BNT162b2 (10 µg) (N[a]=401) n[b] (%)

Abbreviations: CDC = Centers for Disease Control and Prevention; MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. Positive N-binding antibody result at Dose 1, positive NAAT result at Dose 1, or medical history of COVID-19.
e. Negative N-binding antibody result at Dose 1, negative NAAT result at Dose 1, and no medical history of COVID-19.
f. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR Morb Mortal Wkly Rep. 2020;69(32):1081-8 and/or obesity (BMI ≥ 95th percentile).
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (06:55) Source Data: adsl Table Generation: 01APR2022 (14:27) (Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File: ./nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/adsl_s005_demo_p23_1d30_saf

Medical history of the included subjects:

Immune system disorders: 25.4% mostly consisting of a variety of non-drug allergies, also including drug hypersensitivity (2.5%).
Respiratory, thoracic, and mediastinal disorders: 13.0% mostly consisting of asthma (7.7%) and various types of upper airway conditions commonly seen in this age group.
Psychiatric disorders: 12.7% including attention deficit hyperactivity disorder (8.5%), and a variety of behavioural disorders commonly seen in this age group.
Skin and subcutaneous tissue disorders: 9.7% mostly consisting of eczema (7.0%) and various types of dermatitis and skin conditions commonly seen in this age group. History of Henoch-Schoenlein purpura was reported for 1 participant.
Infections and infestations: 7.2% including a variety of viral and bacterial infections commonly seen in this age group. History of COVID-19 was not reported in any participants.
*Nervous system disorder*s: 5.7% including various types of epilepsy, headache, and sensory or developmental disorders commonly seen in this age group.
Cardiac disorders: reported in 3 participants (0.7%) including congestive cardiomyopathy (n=1), supraventricular extrasystoles (n=1), and supraventricular tachycardia (n=1).
Additionally, congenital cardiac conditions were reported including bicuspid aortic valve (n=2), atrial septal defect (n=1), and patent ductus arteriosus (n=1).

4.2.3. Duration of follow up

The median follow-up time after Dose 3 was 1.3 months (range: 1.0 to 1.8 months) (Table 19 below). All participants had a follow-up duration of ≥1 to <2 months after Dose 3.

Table 19. Follow-Up Time After Dose 3 – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)
	BNT162b2 (10 µg) (N[a]=401) n[b] (%)
Time from Dose 3 to cutoff date	
<1 Month	0
≥1 -<2 Months	401 (100.0)
Mean (SD)	1.3 (0.17)
Median	1.3
Min, max	(1.0, 1.8)

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: 01APR2022 (14:26) Source Data: adsl Table Generation: 01APR2022 (14:35) (Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File: ./nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/adsl_fu_d2_p23

Local reactions and systemic events were assessed for Phase 2/3 participants 5 to <12 years of age who received a booster (third) dose of BNT162b2 10-µg for 7 days after each dose, with e-diary data from N=398 after Dose 1, N=399 after Dose 2, and N=371 after Dose 3. There were technical issues impacting activation of the e-diary following Dose 3 that resulted in some participants not recording events on Day 1 post-Dose 3.

Table 20. E-Diary Transmission – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (10 µg)		
	Dose 1	Dose 2	Dose 3
	n[a] (%)	n[a] (%)	n[a] (%)
Vaccinated[b]	401	401	401
E-diary			
Not transmitted[c]	3 (0.7)	2 (0.5)	30 (7.5)
Transmitted[d]			
Day 1	369 (92.0)	346 (86.3)	244 (60.8)
Day 2	377 (94.0)	375 (93.5)	304 (75.8)
Day 3	361 (90.0)	371 (92.5)	310 (77.3)
Day 4	366 (91.3)	371 (92.5)	307 (76.6)
Day 5	371 (92.5)	347 (86.5)	313 (78.1)
Day 6	361 (90.0)	354 (88.3)	322 (80.3)
Day 7	356 (88.8)	347 (86.5)	308 (76.8)
All 7 days[e]	254 (63.3)	232 (57.9)	145 (36.2)

a. n = Number of participants with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. If no data for temperature, local reactions, fever/pain medication, or systemic events are reported for the entire e-diary collection period (Day 1 through Day 7), the e-diary is considered not transmitted.
d. If any data for temperature, local reactions, fever/pain medication, or systemic events are reported for the specified day or set of days (i.e., "all 7 days"), the e-diary is considered transmitted.
e. "All 7 days" includes Day 1 through Day 7 after vaccination. Day 1 is the day of vaccination.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (10:56) Source Data: adfacevd Table Generation: 01APR2022 (14:37)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File:

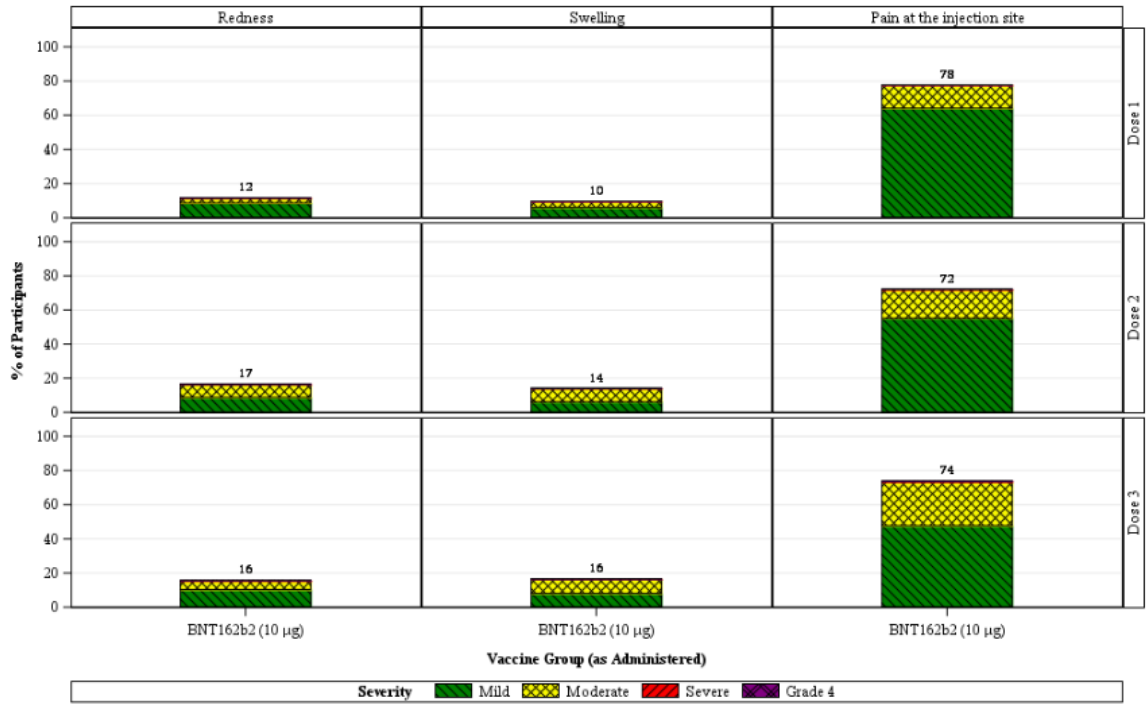
4.3. Results

4.3.1. Reactogenicity

Local reactions

Most local reactions were mild or moderate in severity. Severe local reactions were reported infrequently after each dose (≤1%); severe events after Dose 3 included injection site pain (n=2 [0.5%]) and redness (n=1 [0.3%]). No Grade 4 local reactions were reported after any dose. The median onset for all local reactions after any dose of BNT162b2 10-µg was 1 to 2 days, and all events resolved within a median duration of 1 to 2 days after onset.

Figure 3. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population



Note: The number above each bar denotes the percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (10:56) Source Data: adfacevd Table Generation: 01APR2022 (23:25)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022)

Table 21. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)											
	BNT162b2 (10 µg)											
	Dose 1			Dose 2			Dose 3			Any Dose		
Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
Redness[d]												
Any	398	46 (11.6)	(8.6, 15.1)	399	66 (16.5)	(13.0, 20.6)	371	58 (15.6)	(12.1, 19.7)	401	120 (29.9)	(25.5, 34.7)
Mild	398	34 (8.5)	(6.0, 11.7)	399	35 (8.8)	(6.2, 12.0)	371	38 (10.2)	(7.4, 13.8)	401	67 (16.7)	(13.2, 20.7)
Moderate	398	12 (3.0)	(1.6, 5.2)	399	30 (7.5)	(5.1, 10.6)	371	19 (5.1)	(3.1, 7.9)	401	51 (12.7)	(9.6, 16.4)
Severe	398	0	(0.0, 0.9)	399	1 (0.3)	(0.0, 1.4)	371	1 (0.3)	(0.0, 1.5)	401	2 (0.5)	(0.1, 1.8)
Grade 4	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
Swelling[d]												
Any	398	38 (9.5)	(6.8, 12.9)	399	56 (14.0)	(10.8, 17.8)	371	61 (16.4)	(12.8, 20.6)	401	107 (26.7)	(22.4, 31.3)
Mild	398	24 (6.0)	(3.9, 8.8)	399	25 (6.3)	(4.1, 9.1)	371	30 (8.1)	(5.5, 11.3)	401	48 (12.0)	(9.0, 15.6)
Moderate	398	14 (3.5)	(1.9, 5.8)	399	31 (7.8)	(5.3, 10.8)	371	31 (8.4)	(5.7, 11.7)	401	59 (14.7)	(11.4, 18.6)
Severe	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
Grade 4	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
Pain at the injection site[e]												
Any	398	309 (77.6)	(73.2, 81.6)	399	288 (72.2)	(67.5, 76.5)	371	274 (73.9)	(69.1, 78.3)	401	370 (92.3)	(89.2, 94.7)
Mild	398	255 (64.1)	(59.1, 68.8)	399	220 (55.1)	(50.1, 60.1)	371	177 (47.7)	(42.5, 52.9)	401	221 (55.1)	(50.1, 60.1)
Moderate	398	54 (13.6)	(10.4, 17.3)	399	67 (16.8)	(13.3, 20.8)	371	95 (25.6)	(21.2, 30.4)	401	146 (36.4)	(31.7, 41.3)
Severe	398	0	(0.0, 0.9)	399	1 (0.3)	(0.0, 1.4)	371	2 (0.5)	(0.1, 1.9)	401	3 (0.7)	(0.2, 2.2)
Grade 4	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
Any local reaction[f]	398	315 (79.1)	(74.8, 83.0)	399	296 (74.2)	(69.6, 78.4)	371	278 (74.9)	(70.2, 79.3)	401	373 (93.0)	(90.1, 95.3)

Note: Reactions were collected in the e-diary and unscheduled clinical assessments from Day 1 through Day 7 after each vaccination.
Note: Grade 4 reactions were classified by the investigator or medically qualified person.
a. N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Mild: ≥0.5 to 2.0 cm; moderate: >2.0 to 7.0 cm; severe: >7.0 cm; Grade 4: necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).
e. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe pain at the injection site.
f. Any local reaction: any redness ≥0.5 cm, any swelling ≥0.5 cm, or any pain at the injection site.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (06:55) Source Data: adfacevd Table Generation: 01APR2022 (14:38)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File: ./nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/adce_s010_lr_p23_saf

Systemic events

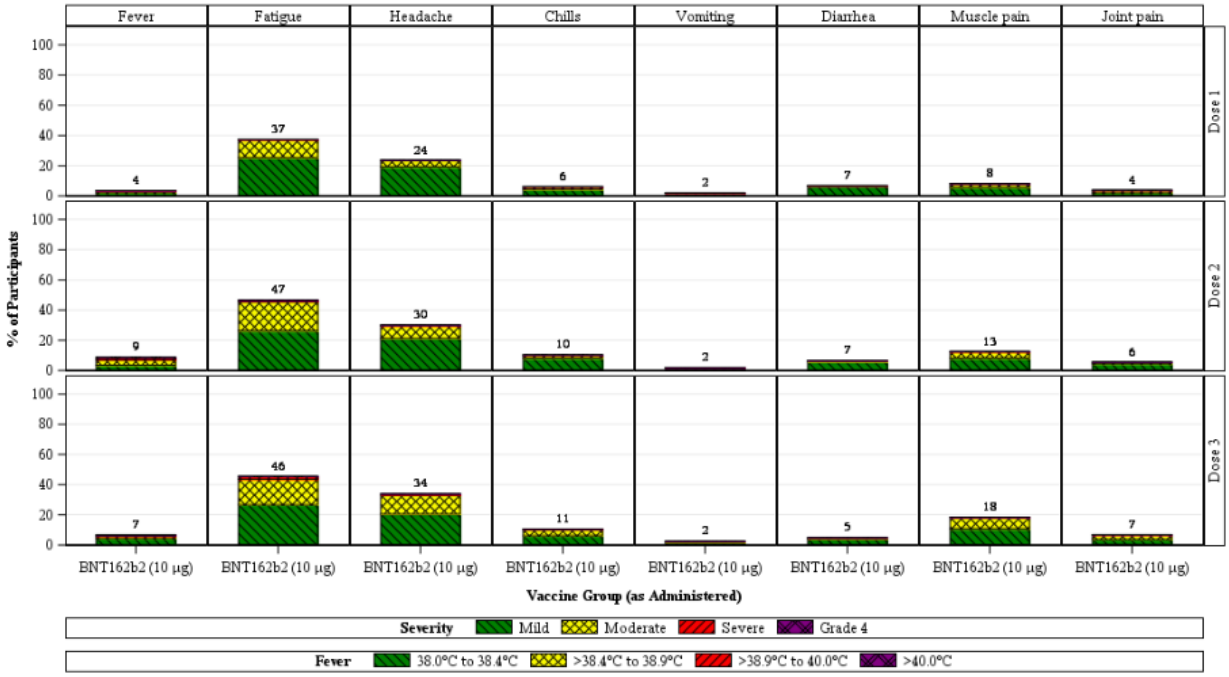
Fatigue was the most frequently reported systemic event reported within 7 days after each dose, followed by headache, and less frequently muscle and joint pain (Figure 4). In general, these events were reported at similar or slightly higher frequencies after Dose 3 compared with after Dose 2. Most systemic events were mild or moderate in severity. Severe systemic events were reported infrequently after each dose (≤2%). Severe systemic events reported after Dose 3 included fatigue (n=7 [1.9%]), headache (n=3 [0.8%]), chills (n=1 [0.3%]), and diarrhoea (n=1 [0.3%]). No Grade 4 events were reported after any dose. No participants reported a fever >40.0 °C after Dose 3. The median onset for most systemic events after any dose of BNT162b2 10-µg was 1 to 2 days, and most events resolved within a median duration of 1 day after onset.

Systemic events in decreasing order of frequency after Dose 3 of BNT162b2 10-µg, as well as antipyretic/pain medication use after each dose, were:

	BNT162b2 (10-µg) Children				**BNT162b2 (30-µg) Adults**			
	Dose 2		Dose 3		Dose 2		Dose 3	
Pain at injection site:	72.2%		73.9%		78.3%		83.0%	
Fatigue:	46.6%		45.6%		61.5%		63.7%	
Headache:	30.1%		34.0%		54.0%		48.4%	

	BNT162b2 (10-µg) Children				BNT162b2 (30-µg) Adults		
Muscle pain:	12.5%		18.3%		39.3%		39.1%
Chills:	10.3%		10.5%		37.8%		29.1%
Joint pain:	5.5%		6.7%		23.8%		25.3%
Fever:	8.8%		6.7%		16.4%		8.7%

Figure 4. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population



Note: Severity was not collected for use of antipyretic or pain medication.
Note: The number above each bar denotes the percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (10:56) Source Data: adfacevd Table Generation: 01APR2022 (23:25)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022)

Table 22. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)											
	BNT162b2 (10 µg)											
	Dose 1			Dose 2			Dose 3			Any Dose		
Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
Fever												
≥38.0°C	398	14 (3.5)	(1.9, 5.8)	399	35 (8.8)	(6.2, 12.0)	371	25 (6.7)	(4.4, 9.8)	401	61 (15.2)	(11.8, 19.1)
≥38.0°C to 38.4°C	398	9 (2.3)	(1.0, 4.2)	399	14 (3.5)	(1.9, 5.8)	371	17 (4.6)	(2.7, 7.2)	401	29 (7.2)	(4.9, 10.2)
>38.4°C to 38.9°C	398	4 (1.0)	(0.3, 2.6)	399	14 (3.5)	(1.9, 5.8)	371	5 (1.3)	(0.4, 3.1)	401	21 (5.2)	(3.3, 7.9)
>38.9°C to 40.0°C	398	1 (0.3)	(0.0, 1.4)	399	6 (1.5)	(0.6, 3.2)	371	3 (0.8)	(0.2, 2.3)	401	10 (2.5)	(1.2, 4.5)
>40.0°C	398	0	(0.0, 0.9)	399	1 (0.3)	(0.0, 1.4)	371	0	(0.0, 1.0)	401	1 (0.2)	(0.0, 1.4)
Fatigue[d]												
Any	398	149 (37.4)	(32.7, 42.4)	399	186 (46.6)	(41.6, 51.6)	371	169 (45.6)	(40.4, 50.8)	401	279 (69.6)	(64.8, 74.0)
Mild	398	101 (25.4)	(21.2, 30.0)	399	105 (26.3)	(22.1, 30.9)	371	99 (26.7)	(22.3, 31.5)	401	124 (30.9)	(26.4, 35.7)
Moderate	398	47 (11.8)	(8.8, 15.4)	399	77 (19.3)	(15.5, 23.5)	371	63 (17.0)	(13.3, 21.2)	401	143 (35.7)	(31.0, 40.6)
Severe	398	1 (0.3)	(0.0, 1.4)	399	4 (1.0)	(0.3, 2.5)	371	7 (1.9)	(0.8, 3.8)	401	12 (3.0)	(1.6, 5.2)
Grade 4	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
Headache[d]												
Any	398	94 (23.6)	(19.5, 28.1)	399	120 (30.1)	(25.6, 34.8)	371	126 (34.0)	(29.2, 39.0)	401	220 (54.9)	(49.8, 59.8)
Mild	398	77 (19.3)	(15.6, 23.6)	399	85 (21.3)	(17.4, 25.7)	371	76 (20.5)	(16.5, 25.0)	401	137 (34.2)	(29.5, 39.0)
Moderate	398	17 (4.3)	(2.5, 6.8)	399	33 (8.3)	(5.8, 11.4)	371	47 (12.7)	(9.5, 16.5)	401	78 (19.5)	(15.7, 23.7)
Severe	398	0	(0.0, 0.9)	399	2 (0.5)	(0.1, 1.8)	371	3 (0.8)	(0.2, 2.3)	401	5 (1.2)	(0.4, 2.9)
Grade 4	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
Chills[d]												
Any	398	24 (6.0)	(3.9, 8.8)	399	41 (10.3)	(7.5, 13.7)	371	39 (10.5)	(7.6, 14.1)	401	80 (20.0)	(16.1, 24.2)
Mild	398	17 (4.3)	(2.5, 6.8)	399	33 (8.3)	(5.8, 11.4)	371	23 (6.2)	(4.0, 9.2)	401	53 (13.2)	(10.1, 16.9)
Moderate	398	7 (1.8)	(0.7, 3.6)	399	7 (1.8)	(0.7, 3.6)	371	15 (4.0)	(2.3, 6.6)	401	25 (6.2)	(4.1, 9.1)
Severe	398	0	(0.0, 0.9)	399	1 (0.3)	(0.0, 1.4)	371	1 (0.3)	(0.0, 1.5)	401	2 (0.5)	(0.1, 1.8)
Grade 4	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
Vomiting[e]												
Any	398	8 (2.0)	(0.9, 3.9)	399	7 (1.8)	(0.7, 3.6)	371	9 (2.4)	(1.1, 4.6)	401	21 (5.2)	(3.3, 7.9)
Mild	398	8 (2.0)	(0.9, 3.9)	399	7 (1.8)	(0.7, 3.6)	371	6 (1.6)	(0.6, 3.5)	401	18 (4.5)	(2.7, 7.0)
Moderate	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	3 (0.8)	(0.2, 2.3)	401	3 (0.7)	(0.2, 2.2)
Severe	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
Grade 4	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
Diarrhea[f]												
Any	398	27 (6.8)	(4.5, 9.7)	399	26 (6.5)	(4.3, 9.4)	371	18 (4.9)	(2.9, 7.6)	401	60 (15.0)	(11.6, 18.8)
Mild	398	26 (6.5)	(4.3, 9.4)	399	23 (5.8)	(3.7, 8.5)	371	15 (4.0)	(2.3, 6.6)	401	53 (13.2)	(10.1, 16.9)
Moderate	398	1 (0.3)	(0.0, 1.4)	399	3 (0.8)	(0.2, 2.2)	371	2 (0.5)	(0.1, 1.9)	401	6 (1.5)	(0.6, 3.2)
Severe	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	1 (0.3)	(0.0, 1.5)	401	1 (0.2)	(0.0, 1.4)
Grade 4	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
New or worsened muscle pain[d]												
Any	398	32 (8.0)	(5.6, 11.2)	399	50 (12.5)	(9.4, 16.2)	371	68 (18.3)	(14.5, 22.6)	401	112 (27.9)	(23.6, 32.6)
Mild	398	23 (5.8)	(3.7, 8.5)	399	33 (8.3)	(5.8, 11.4)	371	40 (10.8)	(7.8, 14.4)	401	70 (17.5)	(13.9, 21.5)
Moderate	398	9 (2.3)	(1.0, 4.2)	399	16 (4.0)	(2.3, 6.4)	371	28 (7.5)	(5.1, 10.7)	401	41 (10.2)	(7.4, 13.6)
Severe	398	0	(0.0, 0.9)	399	1 (0.3)	(0.0, 1.4)	371	0	(0.0, 1.0)	401	1 (0.2)	(0.0, 1.4)
Grade 4	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)

New or worsened joint pain[d]												
Any	398	15 (3.8)	(2.1, 6.1)	399	22 (5.5)	(3.5, 8.2)	371	25 (6.7)	(4.4, 9.8)	401	49 (12.2)	(9.2, 15.8)
Mild	398	9 (2.3)	(1.0, 4.2)	399	18 (4.5)	(2.7, 7.0)	371	14 (3.8)	(2.1, 6.3)	401	31 (7.7)	(5.3, 10.8)
Moderate	398	6 (1.5)	(0.6, 3.3)	399	4 (1.0)	(0.3, 2.5)	371	11 (3.0)	(1.5, 5.2)	401	18 (4.5)	(2.7, 7.0)
Severe	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
Grade 4	398	0	(0.0, 0.9)	399	0	(0.0, 0.9)	371	0	(0.0, 1.0)	401	0	(0.0, 0.9)
Any systemic event[g]	398	202 (50.8)	(45.7, 55.8)	399	230 (57.6)	(52.6, 62.5)	371	220 (59.3)	(54.1, 64.3)	401	328 (81.8)	(77.7, 85.5)
Use of antipyretic or pain medication[h]	398	53 (13.3)	(10.1, 17.1)	399	87 (21.8)	(17.8, 26.2)	371	114 (30.7)	(26.1, 35.7)	401	170 (42.4)	(37.5, 47.4)

Note: Events and use of antipyretic or pain medication were collected in the e-diary and unscheduled clinical assessments from Day 1 through Day 7 after each dose. Grade 4 events were classified by the investigator or medically qualified person.
a. N = number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe fatigue, severe headache, severe chills, severe muscle pain, or severe joint pain.
e. Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration; Grade 4: emergency room visit or hospitalization for severe vomiting.
f. Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours; Grade 4: emergency room visit or hospitalization for severe diarrhea.
g. Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
h. Severity was not collected for use of antipyretic or pain medication.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (10:56) Source Data: adfacevd Table Generation: 01APR2022 (14:39)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File: /nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/adce_s020_se_p23_saf

4.3.2. Adverse Events

Table 23. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 3 to 1 Month After Dose 3 – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)
	BNT162b2 (10 µg) (N[a]=401)
Adverse Event	n[b] (%)
Any adverse event	36 (9.0)
Related[c]	19 (4.7)
Severe	1 (0.2)
Life-threatening	0
Any serious adverse event	0
Related[c]	0
Severe	0
Life-threatening	0
Any nonserious adverse event	36 (9.0)
Related[c]	19 (4.7)
Severe	1 (0.2)
Life-threatening	0
Any adverse event leading to withdrawal	0
Related[c]	0
Serious	0
Severe	0
Life-threatening	0
Death	0

Adverse Event	Vaccine Group (as Administered) BNT162b2 (10 µg) (N[a]=401) n[b] (%)

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 adverse event," n = the number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to the study intervention.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (10:56) Source Data: adae Table Generation: 01APR2022 (15:11) (Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File: ./nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/adae_s091_all_pd2_p23_1d30

This analysis through the cut-off date accounts for a median of 1.3 months of follow-up post-Dose 3 (up to a maximum of 1.8 months post-Dose 3).

Overall, any AEs were reported by 9.0% of participants from Dose 3 to 1 month after Dose 3. Many of the AEs were consistent with reactogenicity events that were reported as AEs (e.g., injection site pain, headache, and fatigue). AE frequencies in SOCs capturing reactogenicity events included:

- General disorders and administration site conditions: 2.2%
- Gastrointestinal disorders: 1.5%
- Nervous system disorders: 1.0%
- Musculoskeletal and connective tissue disorders: 0.5%

In addition to reactogenicity events, most other events reported were infections, illnesses, and injuries typically observed in this age group. Additionally, AEs of clinical interest included cases of lymphadenopathy (including palpable lymph node or axillary mass) which were reported in 10 participants (2.5%), and rash which was reported in 1 participant (0.2%).

Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 3 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population.

No immediate AEs were reported within 30 minutes of receiving Dose 3 of BNT162b2 10 µg.

Related Adverse Events

Table 24. Number (%) of Participants Reporting at Least 1 Related Adverse Event From Dose 3 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (10 µg) (N[a]=401)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Any adverse event	19 (4.7)	(2.9, 7.3)
Blood and lymphatic system disorders	8 (2.0)	(0.9, 3.9)
Lymphadenopathy	8 (2.0)	(0.9, 3.9)
Gastrointestinal disorders	1 (0.2)	(0.0, 1.4)
Diarrhoea	1 (0.2)	(0.0, 1.4)
General disorders and administration site conditions	9 (2.2)	(1.0, 4.2)
Injection site pain	7 (1.7)	(0.7, 3.6)
Fatigue	2 (0.5)	(0.1, 1.8)
Pain	1 (0.2)	(0.0, 1.4)
Pyrexia	1 (0.2)	(0.0, 1.4)
Investigations	1 (0.2)	(0.0, 1.4)
Lymph node palpable	1 (0.2)	(0.0, 1.4)
Musculoskeletal and connective tissue disorders	2 (0.5)	(0.1, 1.8)
Arthralgia	1 (0.2)	(0.0, 1.4)
Axillary mass	1 (0.2)	(0.0, 1.4)
Nervous system disorders	4 (1.0)	(0.3, 2.5)
Headache	3 (0.7)	(0.2, 2.2)
Dizziness	1 (0.2)	(0.0, 1.4)

Note: MedDRA (v24.1) 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 adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (10:56) Source Data: adae Table Generation: 01APR2022 (15:11)
(Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File:

Severe of Life-Threatening Adverse Events

No life-threatening (i.e., Grade 4) AEs were reported after Dose 3. One participant (0.2%) reported a severe AE after Dose 3 of BNT162b2 10-µg:

1. A participant in the 5 to 11 year age group had a fever of 102.2° F (39.0° C) with onset at 1-day post-Dose 3, in addition to concurrent AEs of mild dizziness and mild arthralgia (bilateral legs) that all had an onset of 1-day post-Dose 3 and resolved within 3 days with the use of concomitant medication. This participant also previously had a fever reported in the e-diary after Dose 2, with a duration of 2 days (body temperatures of 39.7° C and 40.3° C on Day 2 and Day 3, respectively).

Serious Adverse Events

No SAEs were reported from Dose 3 up to the data cut-off date (22 March 2022)

Death

No deaths were reported up the data cut-off date (22 March 2022).

Other Significant Adverse Events

Based on previous FDA requests for information on AEs of clinical interest in prior submissions, the following MedDRA Standardized MedDRA Queries (SMQ) were applied to search the safety data: Angioedema, Arthritis, Convulsions, Demyelination, Hypersensitivity, Peripheral Neuropathy, and Vasculitis. There were no PTs associated with these SMQs in children 5 to <12 years of age, except for 1 case of rash (Hypersensitivity SMQ) which is summarized below.
Additionally, from the analysis of AEs (Table 24), there were no AEs of clinical interest reported of anaphylaxis, myocarditis, pericarditis, Bell's palsy (or facial paralysis/paresis), or appendicitis. Other notable pertinent negatives (i.e., no cases reported in this population as of the data cut-off for this submission) included (but were not limited to): arthritis, thrombocytopenic events, thromboembolic or intravascular coagulation events, autoimmune or demyelination events, meningitis, encephalitis, neuritis, peripheral neuropathy, vasculitis, Kawasaki disease, MIS-C, or acute respiratory distress syndrome. The only AE of clinical interest in this safety dataset was lymphadenopathy, which is summarized below:

Lymphadenopathy

Lymphadenopathy is considered an adverse reaction to this vaccine and is noted as such in the product labelling.
From Dose 3 to 1 month after Dose 3, 10 cases of lymphadenopathy (including palpable lymph node or axillary mass) were identified, representing 2.5% of the safety population (Table 24). This frequency of lymphadenopathy after Dose 3 of BNT162b2 10-µg in children 5 to <12 years of age is higher than previously observed after Dose 2 (0.9%), and less than that observed following Dose 3 of BNT162b2 30-µg in adults ≥18 years of age (5.2%). Overall, all cases of lymphadenopathy reported after Dose 3 of BNT162b2 10-µg were mild and considered by the investigator as related to study intervention; most of these cases were identified as occurring in axillary or cervical nodes, had an onset within 2 days of booster vaccination, and were reported as resolved within approximately 1 week after onset.

Rash

Rash is considered an adverse reaction to this vaccine and is noted as such in the product labelling.
From Dose 3 to 1 month after Dose 3, 1 participant (0.2%) reported a rash after booster vaccination. The mild face rash was considered by the investigator as unrelated to study intervention, was attributed to face mask wearing, and had onset at 11 days post-Dost 3 and resolution within 4 days after onset.

Table 25. Selected Standardised MedDRA Queries From Dose 3 to 1 Month After Dose 3 – Participants in 5 to <12 Years of Age – Phase 2/3 – Safety Population

SMQ	Overall SMQ System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (10 µg) (N[a]=401) n[b] (%)
	Participants with any unsolicited adverse events within SMQ	1 (0.25)
Angioedema (SMQ)	Any unsolicited adverse events within Angioedema (SMQ)	0
Arthritis (SMQ)	Any unsolicited adverse events within Arthritis (SMQ)	0
Convulsions (SMQ)	Any unsolicited adverse events within Convulsions (SMQ)	0
Demyelination (SMQ)	Any unsolicited adverse events within Demyelination (SMQ)	0
Hypersensitivity (SMQ)	Any unsolicited adverse events within Hypersensitivity (SMQ)	1 (0.25)
	Skin and subcutaneous tissue disorders	1 (0.25)
	Rash	1 (0.25)
Peripheral neuropathy (SMQ)	Any unsolicited adverse events within Peripheral neuropathy (SMQ)	0
Vasculitis (SMQ)	Any unsolicited adverse events within Vasculitis (SMQ)	0

Abbreviation: SMQ = Standardized MedDRA query.
Note: MedDRA (v24.1) 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 category. For "any unsolicited adverse events within SMQ," n = the number of participants reporting at least 1 occurrence of any unsolicited adverse events within SMQ.
PFIZER CONFIDENTIAL SDTM Creation: 01APR2022 (10:56) Source Data: adae Table Generation: 01APR2022 (16:26) (Cutoff Date: 22MAR2022, Snapshot Date: 31MAR2022) Output File: ./nda2_ubped/C4591007_5LT12_DOSE3_EUA_APR2022/adae_smq_p2_saf_12

4.4. Post-marketing data

4.4.1. Cumulative post-marketing safety data in relation to the use of a booster dose in this population

Cumulatively, out of the 1,474,818[1] post-authorization total reports received through 10 June 2022, there was a total of 10,679 reports involving children aged between 5 years through less than 12 years[2] and 119 post-authorization reports out of these, were reported after receiving a booster dose.[3]

[1] Post-authorisation search criteria.
[2] Included cases reporting a numeric age and cases where a numeric age was not provided but age group was reported as "Child".
[3] Twenty-three (23) cases reported in children exposed through breastfeeding were excluded from the analysis due to indirect exposure.

Table 27 presents the demographic information of the 119 post-authorization reports involving children aged 5 years through less than 12 years of age reporting an AE after a booster dose.

Table 26. Demographic Information – All Post-Authorisation Reports of Individuals aged 5 through less than 12 Years receiving a Booster Dose – Cumulative Data through 10 June 2022

Characteristics		No. of Cases N (%)[a]
Number of cases[e]		119
Gender	Female	46 (38.7)
	Male	44 (37.0)
	No Data	29 (24.4)
Age (years)	n	105
	Min-Max	5.0 – 11.0
Number of cases[e]		119
	Mean	9.0
	Median	10.0
Country of occurrence (≥2% of all cases)	United States (US)	88 (73.9)
	Germany	14 (11.8)
	Canada	5 (4.2)
Case Seriousness	Serious	22 (18.5)
	Non-serious	97 (81.5)
Case Outcome	Fatal	1 (0.8)
	Not resolved	11 (9.2)
	Resolved/Resolving	18 (15.1)
	Unknown	89 (74.8)
Medically Confirmed	Yes	75 (63.0)
	No	44 (37.0)
Medical history (PTs reported more than once) n = 10	Cerebral palsy, Epilepsy	2 each
Co-suspect vaccines (n = 0) Co-suspect medication (n = 1)	Adalimumab	1
Concomitant vaccines (n = 2) Concomitant medications (n = 8)	HPV vaccine [b] Diphtheria vaccine toxoid, pertussis vaccine, tetanus toxoid Meningococcal vaccine [c]	2 each[f]
	Clobazam, valproate [d]	2 each[f]
Booster dose	Homologous	47
	Heterologous	1
	Primary series with an unknown manufacturer	71

a. Due to rounding, sum of percentages may not match 100%.
b. 4-valent and 9-valent in 1 case each.
c. Including ACWY in 1 case.
d. Including semisodium and sodium.
e. There were 13 unlocked cases. Unlocked cases are those cases either in the DSU, Primary Review or the Medical Review workflows that are not yet in the Distribution workflow which locks the cases and the system automatically runs reporting rules, schedules and subsequently generates expedited reports as appropriate.
f. Only concomitant vaccines and medications reported at least twice.

Table 27. Age Distribution by Gender

Age / Gender	5 Years n	6 Years n	7 Years n	8 Years n	9 Years n	10 Years n	11 Years n	Child[a] n	Total N = 119
Female	2	3	3	8	4	14	11	1	46
Male	2	4	9	3	3	9	13	1	44
Unknown	0	4	1	2	2	4	4	12	29
All n (%)	4 (3.4)	11 (9.2)	13 (10.9)	13 (10.9)	9 (7.6)	27 (22.7)	28 (23.5)	14 (11.8)	119

a. Age value not provided. "Child" includes individuals aged 2 through 12 years.
n: Number of cases; (%): percentage: n/N

A total of 309 AEs (of which 54 serious and 255 non-serious) was reported in these 119 cases.

The MedDRA SOCs containing the greatest number of events (≥3 occurrences) were Injury, poisoning and procedural complications (160 events), General disorders and administration site conditions (52 events), Surgical and medical procedures and Musculoskeletal and connective tissue disorders (12 events each), Infections and infestations (11 events), Gastrointestinal disorders and Nervous system disorders (10 events each), Investigations (8 events), Skin and subcutaneous tissue disorders, Cardiac disorders and Respiratory, thoracic and mediastinal disorders (7 events each), Blood and lymphatic system disorders and Product issues (3 events each).

Table 29 shows the clinical events reported more than twice (MedDRA v. 25.0) by SOC and by seriousness category. Of the 119 cases, there were 95 cases coding "at-risk events", 76 of which had no associated AEs. The "at-risk event" terms[4] reported more than twice, included: Poor quality product administered (34), Product administration error (29), Overdose (23), Product administered to patient of inappropriate age (20), Off label use (16), Product preparation error (15), Immunisation (12), Product use issue (6), Drug ineffective (5), Expired product administered (4), Incorrect dose administered, Product temperature excursion issue and Vaccination failure (3 each). In the remaining 43 cases, there were 126 clinical adverse events; of these, 36 were serious and 90 were non-serious.

[4] More than 1 at-risk PT in some cases.

Table 28. Clinical Events (≥2) by SOC and Event Seriousness

SOCs[a] (Total No. of PTs)	PTs	Serious	Non-Serious
General disorders and administration site conditions (44)	Pyrexia	3	10
	Fatigue	0	9
	Vaccination site pain	0	4
	Chest pain	2	1
	Axillary pain	2	0
	Malaise	0	2
	Pain	1	1
	Swelling	2	0
	Other PTs	0	7
Musculoskeletal and connective tissue disorders (12)	Pain in extremity	0	5
	Other PTs	3	4
Infections and infestations (11)	COVID-19	7	0
	Other PTs	2	2
Gastrointestinal disorders (10)	Abdominal pain	0	2
	Abdominal pain upper	0	2
	Diarrhoea	0	2
	Other PTs	1	3
Nervous system disorders (10)	Headache	0	2
	Migraine	0	2
	Other PTs	2	4
Cardiac disorders (7)	Myocarditis	2	0
	Other PTs	2	3
Respiratory, thoracic and mediastinal disorders (7)	Dyspnoea	3	0
	Nasal congestion	0	2
	Other PTs	0	2
Skin and subcutaneous tissue disorders (7)	Rash	1	2
	Urticaria	0	2
	Other PTs	0	2
Blood and lymphatic system disorders (3)	Lymphadenopathy	1	2

At risk terms are not included in this table.

a. Other SOCs containing single clinical events include Investigations (8), Vascular disorders (2), Ear and labyrinth disorders, Eye disorders, Immune system disorders, Psychiatric disorders and Renal and urinary disorders (1 each).

Information on the BNT162b2 dosage administered to paediatric patients 5 years to less than 12 years was reported as follows:

- Adult dosage/formulation (information was provided in the narrative and/or in the Verbatim as "Adult dose/Adult formulation or Purple/Grey cap" or the dose was 0.3 mL): 23 cases
    - In 9 non-serious cases an Overdose was reported; in 7 cases no additional clinical events were co-reported, while in the 2 remaining cases Pyrexia (2), Erythema, Feeling hot, Lymphadenopathy and Pain (1 each) were co-reported.
    - In 5 cases, of which 2 were serious, clinical events[5] were reported upon administration of the booster dose.
    - In the remaining 9 non-serious cases only at-risk terms indicative of medication errors and/or off-label used were reported with no clinical adverse events.

[5] Including 1 case of Myocarditis and 1 case of Multisystem inflammatory syndrome in children.

- Paediatric dosage/formulation (including cases where the adult dosage/formulation was not administered, or information was provided in the narrative and/or in the Verbatim as "Orange cap/Tris" or the dose was reported as 10 micrograms / 0.2 mL): 96 cases
    - In 15 non-serious cases an Overdose was reported as the vaccine was administered either undiluted or with wrong dilution. No additional clinical events were co-reported in these cases.
    - In 36 cases, of which 16 were serious, clinical events[6] were reported upon administration of the booster dose.
    - In the remaining 45 non-serious cases[7] only at-risk terms indicative of medication errors and/or off-label used were reported with no clinical adverse events.

Serious cases of note

Out of the 18 serious cases, 5 cases where the seriousness criterion was reported as Hospitalization Required or Death are summarized below.

- **Fatal case (1 consumer case received through the Regulatory Authority)**

The fatal case, from a non-contactable consumer, refers to a patient in an EU country in the 5 to 11 years age group and contains very little information. This child was reported to have received a dose of BNT162b2 as a booster dose (PTs: Off label use, Product administered to patient of inappropriate age), after a primary series from an unknown manufacturer. Dyspnoea occurred 69 days after the booster dose; the child died on an unknown date due to dyspnoea. It was unknown if an autopsy was performed. The report was assessed as Unclassifiable by PEI.

- **Myocarditis (2 Health Care Professional cases received through the Regulatory Authority)**

- A patient in an EU country in the 5-to-11-year age group received a dose 3 (0.3 mL) of BNT162b2. Three (3) days later, while exercising, the child experienced sudden precordial chest pain associated with breathlessness lasting 30 minutes. The child was hospitalised for myocarditis and several non-serious clinical events (Troponin abnormal, Hyperaemia, Chromaturia, Protein urine present, Urine ketone body present, pH urine increased, Sinus arrhythmia, Left ventricular hypertrophy, Electrocardiogram abnormal and Blood urine present) were reported. Myocarditis resolved after 1 day. It was also reported but not elaborated on that "a possible minimal myocardial rupture" occurred with onset in the same month of the booster dose, resolved quickly and spontaneously and was thought to be related to sports. Medical history and concomitant medications were not reported.
- A patient in an EU country in the 5-to-11-year age group received a booster dose of BNT162b2 21 days after a primary series from an unknown manufacturer. Probable subclinical myocarditis (PT Myocarditis) and Troponin increased were reported on an unknown date; Chest pain with Dyspnoea were reported 10 days after the booster dose and Chest pain and Palpitations were reported 13 days after the booster dose. No other patient detail was provided (ie, diagnostic tests, medical history, concomitant medications, course of the event). The patient recovered at the time of the reporting.

- **Guillain-Barre syndrome (1 consumer case)**

[6] Including 1 case with fatal outcome (Off label use, Immunisation, Dyspnoea, Product administered to patient of inappropriate age), 1 case of Myocarditis; 8 cases of Drug ineffective/Vaccination failure and COVID-19/ Suspected COVID-19; 1 case of Guillain-Barre syndrome, 2 cases indicative of swelling (Bone swelling/Parotid gland enlargement and Axillary pain/Swelling), and 1 case each of Lymphadenopathy, Syncope and Pyrexia/Abdominal pain.
[7] There were 4 unlocked serious cases, part of cluster of 5 cases coding the PTs Product administration error, Poor quality product administered; these cases were re-assessed as non-serious cases after the DLP.

- An individual of unknown gender from an Asia/Pacific region country in the 5-to-11-year age group received a booster dose (dose number unknown) with BNT162b2 after a primary series from an unknown manufacturer; medical history and concomitant medications were not reported. On an unknown date the child was diagnosed with Guillain-Barré syndrome and was hospitalised. Diagnostic studies and clinical details were not provided, and the clinical outcome was unknown.

- **Multisystem inflammatory syndrome in children (1 consumer case received through the Regulatory Authority)**

- A patient in an EU country in the 5-to-11-year age group (details on medical history and concomitant medication not provided), received as booster dose 0.3 mL of BNT162b2 after a primary vaccination series from an unknown manufacturer. The same day of the administration of the booster dose, the child developed Multisystem inflammatory syndrome (MIS-C) and was hospitalised; Rash and Pyrexia occurred 23 days after the booster dose. The following non-serious PTs were also reported, with an unknown onset date and clinical outcome: Abdominal pain, Fatigue and Pallor. Rash and pyrexia resolved after treatment with intravenous immune globulin, prednisolone and acetylsalicylic acid. MIS-C was reported as resolved on an unknown date. The report was assessed as Unclassifiable by PEI.

MAH Conclusion

Review of the cumulative available post-marketing data in individuals aged 5 to less than 12 years, did not identify any additional or unexpected risks associated with administration of BNT162b2 and is consistent with the favorable benefit risk balance observed in the clinical study. Post-marketing surveillance activities will continue.

4.4.2. The number of administered and distributed booster doses and observed AEs

It is not possible to discriminate how many doses of the BNT162b2 vaccine paediatric tris-sucrose presentation (10 micrograms/dose) out of 4,331,200 shipped to the US between 17 May 2022 and 22 June 2022 were administered as primary series or as booster doses in individuals aged 5 to less than 12 years.

Considering that up to now BNT162b2 was the only vaccine authorized in the US as a booster in individuals aged 5 to less than 12 years, as per the information available at the US CDC COVID Data Tracker,[8] it is estimated that 497,632 individuals aged 5 to less than 12 years had received a booster dose of BNT162b2 vaccine in the US as of 22 June 2022. These publicly available data may be more indicative of the actual exposure in persons compared to the shipped doses, however it should be noted that these data may also be incomplete.

4.5. Discussion

The safety database constitutes of 401 subjects aged 5-<12 years of which a vast majority received their booster dose 8-9 months post dose 2 (87%). Based on this data, the MAH has proposed that the booster dose should be administered at least six months after dose 2. None of the participants were excluded from the safety population for other reasons. Local and systemic reactogenicity was recorded for 7 days after each dose administration using an electronic diary (e-diary). AEs were collected from Dose 3 to 1 month after Dose 3 and serious AEs (SAEs) are collected from Dose 3 to 6 months after Dose 3.

[8] Centers for Disease Control and Prevention (CDC). COVID Data Tracker. Available at: https://covid.cdc.gov/covid-data-tracker/#vaccinations/CDC COVID Data Tracker (accessed: 24 June 2022).

Duration of follow up was 1-2 months for all 401 subjects. Reactogenicity data after dose 3 is available for 371 subjects. According to the MAH, there were technical issues in activation of the e-diary after dose 3, and therefore data from Day 1 is only available in 244 of the subjects. It is noted that the there is a significantly lower response rate in the e-diary after dose 3 compared to dose 1 and 2 due to technical issues with the e-diary, where about 25% of individuals do not have entries in the e-dairy from day 1 up to day 7 resulting in only 36.2% of the participants having a complete record for all 7 days.

The most common local reaction was pain at injection site (74%), which is in line with what has been observed for dose 2. Most of the local reactions were mild to moderate in intensity. One severe event of redness and two severe events of pain at injection site were reported after dose 3.

Fatigue (46%), followed by headache (34%) was the most commonly reported systemic reaction after dose 3. Fever was reported in 7%, of which 3 subjects reported a body temperature >38.9°C, thus classified as severe. No grade 4 events were reported after dose 3. One event of diarrhoea, one event of chills, three events of headache and 7 events of fatigue were classified as severe.

Antipyretic pain medication was used by 31%, which is a higher frequency compared to dose 2 (22%) and dose 1 (13%).

For AEs, the follow up time covers a median of 1.3 months post-dose 3. The AE profile is overall acceptable and consistent with the known side effect profile of Comirnaty. AEs were reported by overall 9.0% of participants from Dose 3 to 1 month after Dose 3. AEs were in the majority consistent with reactogenicity events, belonging to the SOCs "General disorders and administration site conditions" (2.2%), "Gastrointestinal disorders" (1.5%), "Nervous system disorders" (1.0%) and "Musculoskeletal and connective tissue disorders" (0.5%). To mention are also cases of lymphadenopathy, reported in 10 participants (2.5%), and rash, reported in 1 participant (0.2%). No immediate AEs were reported within 30 minutes of receiving Dose 3 of BNT162b2 10 µg.

Related AEs (4,7%) belong as well to the group of reactogenic events and reflect the known side effect profile of the vaccine, with events such as injection site pain, pyrexia, lymphadenopathy and diarrhoea.

No SAEs, life threatening events or deaths were reported. One severe AE (pyrexia of 39.0C in a participant in the 5- to 11-year-old age group) was reported one day post-dose 3, which resolved within 3 days.

The MAH performed a search on AESIs and detected only two PTs to mention: (1) lymphadenopathy as observed in 10 participants and, thus, higher in frequency (2.5%) than after dose 2 (0.9%) (overall mild in severity, resolving approximately 1 week after onset) and (2) rash as observed in 1 participant 11 days after booster vaccination (mild face rash which was considered unrelated to vaccination by the study physician due to alternative explanation (face mask wearing)).

It is noted that FDA has recently approved booster dose for children aged 5-<12 years, the MAH has provided available post-marketing safety data (cut off date 10 July 2022) in relation to the use of a booster dose in this population.

Overall, the side effect profile after booster dose is consistent with the safety profile known for primary series of Comirnaty 10 µg administered to individuals aged 5-<12 years of age.

5. Changes to the Product Information

As a result of this variation, sections 4.2, 4.8 and 5.1 of the SmPC of COMIRNATY 10 µg are being updated. The Package Leaflet (PL) is updated accordingly.

6. Request for supplementary information

6.1. Other concerns

Clinical aspects

Efficacy

1. Due to the changed COVID-19 epidemiological situation along with the very transmittable omicron variants, many children have now experienced SARS-COV-2 infection. This has caused a reduction of the SARS-COV-2 naïve population. At the same time, MAH have had limited blood sample collection for immunogenicity evaluation after Dose 1 and 2. Due to these reasons the sample size for immunogenicity populations to evaluate dose 3 are smaller than expected. We suggest describing in SmPC only through "Total" population GMT values as it is confusing with different immunogenicity sets with small sample size and unexpected statistically significant different values between 2-dose set and 3- dose set after 1 month post dose 2.

   Suggestion for a simplified Table 7 in SmPC

Assay	**Dose/ sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**
SARS-CoV-2 neutralization assay - NT50 (titre)	1 month Prevax	146	20.5 (20.5, 20.5)
	1 month after Dose 2	96	1253.9 (1116.0, 1408.9)
	3 months Prevax	67	271.0 (229.1, 320.6)
	1 month after Dose 3	67	2720.9 (2280.1, 3247.0)
	GMR post dose 3/2	96/67	2.17 (1.76, 2.68)

2. The Omicron neutralization data after dose 3 relies on 17 subjects and is measured using a non-validated assay. Therefore, please remove this chapter in SmPC.

3. The booster dose induced neutralizing titres against the omicron BA.1 strain which were approx. 1.9-fold higher than those observed after primary vaccination against the index strain (GMT 614 versus 323). As the BA.1 omicron lineage has been replaced by BA.2.12.1, BA.4 and BA.5 lineages, it would be of interest to confirm that the immunogenicity of the booster dose as documented by titres against the no longer circulating BA.1 remain valid/true for the currently circulating BA.2.12.1, BA.4 and BA.5 lineages. This can be done by using the children sera from the immunobridging trial to perform in vitro neutralization assays against omicron BA.2.12.1, BA.4 and BA.5 lineages to allow a comparison between omicron subspecies.

   The MAH is therefore asked to provide a plan and timelines for the availability of data regarding other omicron VOCs i.e. BA.2, BA.4 and BA.5.

4. Taking into consideration the current SmPC recommendations in individuals 12 years of age and older, the MAH is invited to consider the minimum boosting interval

Safety

1. According to the MAH, there were technical issues in activation of the e-diary after dose 3, and therefore data from Day 1 is only available in 244 of the subjects. It is noted that the there is a significantly lower response rate in the e-diary after dose 3 compared to dose 1 and 2, where about 25% of individuals do not have entries in the e-dairy from day 1 up to day 7 resulting in only 36.2% of the participants having a complete record for all 7 days. The MAH is requested to further explain these considerably lower numbers and the discrepancy in reporting between primary series and booster dose.

2. According to the MAH, 311 individuals out of 401 individuals (77%) completed the 1-month post-dose visit, but in the tables where AEs as observed 1 month after booster vaccination are presented the MAH refers to all 401 individuals. The MAH is requested to explain this discrepancy.

3. It is noted that FDA has recently approved a booster dose for children aged 5-<12 years. The MAH is asked to submit all available post-marketing safety data in relation to the use of a booster dose in this population. Both the number of administered and distributed booster doses and observed AEs should be described and evaluated.

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

7.1. Other concerns

Clinical aspects

Efficacy

Question 1

Due to the changed COVID-19 epidemiological situation along with the very transmittable omicron variants, many children have now experienced SARS-COV-2 infection. This has caused a reduction of the SARS-COV-2 naïve population. At the same time, MAH have had limited blood sample collection for immunogenicity evaluation after Dose 1 and 2. Due to these reasons the sample size for immunogenicity populations to evaluate dose 3 are smaller than expected. We suggest to describe in SmPC only through "Total" population GMT values as it is confusing with different immunogenicity sets with small sample size and unexpected statistically significant different values between 2-dose set and 3- dose set after 1 month post dose 2.

Suggestion for a simplified Table 7 in SmPC

Assay	**Dose/ sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**
SARS-CoV-2 neutralization assay - NT50 (titre)	1 month Prevax	146	20.5 (20.5, 20.5)
	1 month after Dose 2	96	1253.9 (1116.0, 1408.9)
	3 months Prevax	67	271.0 (229.1, 320.6)

	1 month after Dose 3	67	2720.9 (2280.1, 3247.0)
	GMR post dose 3/2	96/67	2.17 (1.76, 2.68)

Summary of the MAH's response:

The Sponsor accepts the proposal to simplify Table 30 and further proposes to revise the Table 30 to align the column headers with GMT and GMR data appropriately. The pre-dose information has been excluded from the Table now that GMR has been included as it is less important and not part of the overall comparison.

Table 30: Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

	Sampling time point[a]		
Assay	**1 month after booster dose (n[b]=67) GMT[c] (95% CI[c])**	**1 month after dose 2 (n[b]=96) GMT[c] (95% CI[c])**	**1 month after booster dose/ 1 month after dose 2 GMR[d] (95% CI[d])**
SARS-CoV-2 neutralization assay - NT50 (titre)	2720.9 (2280.1, 3247.0)	1253.9 (1116.0, 1408.9)	2.17 (1.76, 2.68)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student's t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post–Booster Dose minus 1-Month Post–Dose 2) and the corresponding CI (based on the Student's t distribution).

Assessment of the MAH's response:

The changed table is acceptable.

Conclusion

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

☒No need to update overall conclusion and impact on benefit-risk balance

Question 2

The Omicron neutralization data after dose 3 relies on 17 subjects and is measured using a non-validated assay. Therefore, please remove this chapter in SmPC

Summary of the MAH's response: The Omicron neutralization data was a descriptive analysis in a subset of participants, which demonstrated a substantial increase in Omicron neutralizing titers after Dose 3, similar to observations in adults. Prior descriptive analyses have used a similar non-validated assay for characterization of SARS-CoV-2 variant neutralization. Pfizer and BioNTech accept the deletion of text and

table and further proposes to include a summary statement for transparency and further information for the HCP.

New statement in SmPC:

Using a non-validated fluorescence focus reduction neutralization test assay against the Omicron variant of SARS-CoV-2 (B.1.1.529), the NT50 GMT at 1 month after the booster dose among a subset of 17 study participants (614.4 [95% CI: 410.7, 919.2]) was increased compared to the NT50 GMT at 1 month after dose 2 among a subset of 29 study participants (27.6 [95% CI: 22.1, 34.5]).

Assessment of the MAH's response

The summary statement in SmPC is not acceptable. According to ETF input, data obtained with an unvalidated assay should be removed.

The MAH have updated the SmPC accordingly by removing the omicron statement from the SmPC accordingly.

Conclusion

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

☒No need to update overall conclusion and impact on benefit-risk balance

Question 3

The booster dose induced neutralizing titres against the omicron BA.1 strain which were approx. 1.9-fold higher than those observed after primary vaccination against the index strain (GMT 614 versus 323). As the BA.1 omicron lineage has been replaced by BA.2.12.1, BA.4 and BA.5 lineages, it would be of interest to confirm that the immunogenicity of the booster dose as documented by titres against the no longer circulating BA.1 remain valid/true for the currently circulating BA.2.12.1, BA.4 and BA.5 lineages. This can be done by using the children sera from the immunobridging trial to perform in vitro neutralization assays against omicron BA.2.12.1, BA.4 and BA.5 lineages to allow a comparison between omicron subspecies.

The MAH is therefore asked to provide a plan and timelines for the availability of data regarding other omicron VOCs i.e. BA.2, BA.4 and BA.5.

Summary of the MAH's response

Administration of a booster (third) dose of BNT162b2 10-µg elicited robust neutralizing titers against the wild-type variant of SARS-CoV-2 in an evaluable immunogenicity population of 67 children 5 to <12 years of age who were without evidence of SARS-CoV-2 infection. Robust neutralizing GMTs were observed at 1-month post-Dose 3 that were substantially increased (2720.9) compared with those at 1-month post-Dose 2 (1253.9) and prior to booster (Dose 3) vaccination (271.0).

A supportive analysis using a fluorescent focus reduction neutralization test assay evaluated neutralizing GMTs against a recombinant SARS-CoV-2 Omicron variant and recombinant wild-type (reference) strain in an evaluable immunogenicity population of 29 children 5 to <12 years of age who were without evidence of prior SARS-CoV-2 infection and had assay data available at both 1-month post-Dose 2 and 1-month post-Dose 3. At 1-month post-Dose 2, the neutralizing GMTs for the Omicron variant and reference strain were 27.6 and 323.8, respectively. By 1-month post-Dose 3, the neutralizing GMTs for Omicron and reference were 614.4 and 1702.8, respectively, representing a substantial 22-fold increase for the recombinant Omicron variant and from the post-two-dose primary series (1-month post-Dose 2 data) to post-booster vaccination, as well as a 5-fold for the recombinant reference strain.

Neutralization of Omicron sublineages, including BA.2, BA.2.12.1, and BA.4/BA.5 has been evaluated in sera from the phase 1 participants 23 to 74 years of age in the C4591001 pivotal study. BNT162b2 post-Dose 3 immune sera neutralized USA-WA1/2020, Omicron BA.1-, BA.2-, BA.2.12.1-, BA.3-, BA.4/5-, and XD-spike SARS-CoV-2s with geometric mean titers (GMTs) of 1335, 393, 298, 315, 216, 103, and 301, respectively; thus, BA.4/5 SARS-CoV-2 spike variant showed the highest propensity to evade vaccine neutralization compared to the original Omicron variants BA.1. As neutralization trends against the reference strain (USA-WA-1/2020) and Omicron BA.1 have been consistent across age groups (adults and 5-11-year olds), we would anticipate similar trends against the Omicron sublineages as shown in Kuhade et al.v

Testing is not planned in the 5-11-year-old age group as data in this age group have been consistent with what has been observed in the adult population.

Assessment of the MAH's response: The answer is acceptable. Neutralization against other lineages including currently circulation Omicron BA4/5 is expected to be lower than against Wuhan or Omicron BA1.

Conclusion

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

☒No need to update overall conclusion and impact on benefit-risk balance

Question 4
Taking into consideration the current SmPC recommendations in individuals 12 years of age and older, the MAH is invited to consider the minimum boosting interval.

Summary of the MAH's response

The sponsor acknowledges the comment; however the data supports a dosing interval of at least 6 months from the primary series to the booster dose.

Assessment of the MAH's response: Agreed with MAH to recommend for a booster an interval at least 6 months from dose 2

Conclusion

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

☒No need to update overall conclusion and impact on benefit-risk balance

Safety

Question 1
According to the MAH, there were technical issues in activation of the e-diary after dose 3, and therefore data from Day 1 is only available in 244 of the subjects. It is noted that the there is a significantly lower response rate in the e-diary after dose 3 compared to dose 1 and 2, where about 25% of individuals do not have entries in the e-dairy from day 1 up to day 7 resulting in only 36.2% of the participants having a complete record for all 7 days. The MAH is requested to further explain these considerably lower numbers and the discrepancy in reporting between primary series and booster dose.

Summary of the MAH's response
The technical issue in app activation was identified after the initiation of Dose 3 implementation for which only 32 out of the entire 425 participants included did not complete the e-diary for all 7 days due to this issue. Protocol deviations were reported for these participants. Given the limited impact, the compliance issues noted above are not reflective of this technical issue. Although the overall 7 days compliance was lower than Dose 1 and 2, the daily compliance for Dose 3 remained above 75% from Day 2 onwards.

Assessment of the MAH's response
The lower response rate after dose 3 compared to dose 1 and 2 is according to the MAH due to technical issue with the e-diary system after dose 3. It would of course have been of value with to have access to all possible data, especially in limited study size as this. However, the response rate was at about 75% from D2.

The issue is not pursued.

Conclusion

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

☒No need to update overall conclusion and impact on benefit-risk balance

Question 2
According to the MAH, 311 individuals out of 401 individuals (77%) completed the 1-month post-dose visit, but in the tables where AEs as observed 1 month after booster vaccination are presented the MAH refers to all 401 individuals. The MAH is requested to explain this discrepancy.

Summary of the MAH's response
Adverse events were summarized for the safety population which included all participants who received the booster dose. Among the 401 participants in the safety population, 311 completed a 1-month post-Dose visit by the cutoff date. Of note, although there were 90 participants that didn't complete the 1-month post-Dose visit by the cutoff date, they all received the booster dose at least 1 month prior to the cutoff date and remained in the study. The AE summary included all AEs reported up to the 1-month post-Dose visit for the 311 participants who completed 1-month post-Dose visit and all available AEs reported up to the cutoff date for the 90 participants who didn't complete the 1-month post-Dose visit by the cutoff date.

Assessment of the MAH's response
The answer of the MAH is accepted. Issue resolved.

Conclusion

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

☒No need to update overall conclusion and impact on benefit-risk balance

Question 3
It is noted that FDA has recently approved a booster dose for children aged 5-<12 years. The MAH is asked to submit all available post-marketing safety data in relation to the use of a booster dose in this

population (a). Both the number of administered and distributed booster doses and observed AEs should be described and evaluated (b).

Summary of the MAH's response

a. Cumulative post-marketing safety data in relation to the use of a booster dose in this population

Cumulatively, out of the 1,474,818[9] post-authorization total reports received through 10 June 2022, there was a total of 10,679 reports involving children aged between 5 years through less than 12 years[10] and 119 post-authorization reports out of these, were reported after receiving a booster dose.[11]

Table 31 below presents the demographic information of the 119 post-authorization reports involving children aged 5 years through less than 12 years of age reporting an AE after a booster dose.

Table 31. Demographic Information – All Post-Authorisation Reports of Individuals aged 5 through less than 12 Years receiving a Booster Dose – Cumulative Data through 10 June 2022

Characteristics		No. of Cases N (%)[a]
Number of cases[e]		119
Gender	Female	46 (38.7)
	Male	44 (37.0)
	No Data	29 (24.4)
Age (years)	n	105
	Min-Max	5.0 – 11.0
Number of cases[e]		119
	Mean	9.0
	Median	10.0
Country of occurrence (≥2% of all cases)	United States (US)	88 (73.9)
	Germany	14 (11.8)
	Canada	5 (4.2)
Case Seriousness	Serious	22 (18.5)
	Non-serious	97 (81.5)
Case Outcome	Fatal	1 (0.8)
	Not resolved	11 (9.2)
	Resolved/Resolving	18 (15.1)
	Unknown	89 (74.8)
Medically Confirmed	Yes	75 (63.0)
	No	44 (37.0)
Medical history (PTs reported more than once) n = 10	Cerebral palsy, Epilepsy	2 each
Co-suspect vaccines (n = 0) Co-suspect medication (n = 1)	Adalimumab	1
Concomitant vaccines (n = 2) Concomitant medications (n = 8)	HPV vaccine [b] Diphtheria vaccine toxoid, pertussis vaccine, tetanus toxoid Meningococcal vaccine [c]	2 each[f]
	Clobazam, valproate [d]	2 each[f]
Booster dose	Homologous	47
	Heterologous	1
	Primary series with an unknown manufacturer	71

a. Due to rounding, sum of percentages may not match 100%.
b. 4-valent and 9-valent in 1 case each.
c. Including ACWY in 1 case.
d. Including semisodium and sodium.
e. There were 13 unlocked cases. Unlocked cases are those cases either in the DSU, Primary Review or the Medical Review workflows that are not yet in the Distribution workflow which locks the cases and the system automatically runs reporting rules, schedules and subsequently generates expedited reports as appropriate.
f. Only concomitant vaccines and medications reported at least twice.

Table 32. Age Distribution by Gender

[9] Post-authorisation search criteria.
[10] Included cases reporting a numeric age and cases where a numeric age was not provided but age group was reported as "Child".
[11] Twenty-three (23) cases reported in children exposed through breastfeeding were excluded from the analysis due to indirect exposure.

Age Gender	5 Years n	6 Years n	7 Years n	8 Years n	9 Years n	10 Years n	11 Years n	Child[a] n	Total N = 119
Female	2	3	3	8	4	14	11	1	46
Male	2	4	9	3	3	9	13	1	44
Unknown	0	4	1	2	2	4	4	12	29
All n (%)	4 (3.4)	11 (9.2)	13 (10.9)	13 (10.9)	9 (7.6)	27 (22.7)	28 (23.5)	14 (11.8)	119

a. Age value not provided. "Child" includes individuals aged 2 through 12 years.
n: Number of cases; (%): percentage: n/N

A total of 309 AEs (of which 54 serious and 255 non-serious) was reported in these 119 cases.

The MedDRA SOCs containing the greatest number of events (≥3 occurrences) were Injury, poisoning and procedural complications (160 events), General disorders and administration site conditions (52 events), Surgical and medical procedures and Musculoskeletal and connective tissue disorders (12 events each), Infections and infestations (11 events), Gastrointestinal disorders and Nervous system disorders (10 events each), Investigations (8 events), Skin and subcutaneous tissue disorders, Cardiac disorders and Respiratory, thoracic and mediastinal disorders (7 events each), Blood and lymphatic system disorders and Product issues (3 events each).

Table 33 shows the clinical events reported more than twice (MedDRA v. 25.0) by SOC and by seriousness category. Of the 119 cases, there were 95 cases coding "at-risk events", 76 of which had no associated AEs. The "at-risk event" terms[12] reported more than twice, included: Poor quality product administered (34), Product administration error (29), Overdose (23), Product administered to patient of inappropriate age (20), Off label use (16), Product preparation error (15), Immunisation (12), Product use issue (6), Drug ineffective (5), Expired product administered (4), Incorrect dose administered, Product temperature excursion issue and Vaccination failure (3 each). In the remaining 43 cases, there were 126 clinical adverse events; of these, 36 were serious and 90 were non-serious.

Table 33. Clinical Events (≥2) by SOC and Event Seriousness

SOCs[a] (Total No. of PTs)	PTs	Serious	Non-Serious
General disorders and administration site conditions (44)	Pyrexia	3	10
	Fatigue	0	9
	Vaccination site pain	0	4
	Chest pain	2	1
	Axillary pain	2	0
	Malaise	0	2
	Pain	1	1
	Swelling	2	0
	Other PTs	0	7
Musculoskeletal and connective tissue disorders (12)	Pain in extremity	0	5
	Other PTs	3	4
Infections and infestations (11)	COVID-19	7	0
	Other PTs	2	2
Gastrointestinal disorders (10)	Abdominal pain	0	2
	Abdominal pain upper	0	2
	Diarrhoea	0	2
	Other PTs	1	3
Nervous system disorders (10)	Headache	0	2
	Migraine	0	2
	Other PTs	2	4
Cardiac disorders (7)	Myocarditis	2	0
	Other PTs	2	3
Respiratory, thoracic and mediastinal disorders (7)	Dyspnoea	3	0
	Nasal congestion	0	2
	Other PTs	0	2
Skin and subcutaneous tissue disorders (7)	Rash	1	2
	Urticaria	0	2
	Other PTs	0	2
Blood and lymphatic system disorders (3)	Lymphadenopathy	1	2

At risk terms are not included in this table.
a. Other SOCs containing single clinical events include Investigations (8), Vascular disorders (2), Ear and labyrinth disorders, Eye disorders, Immune system disorders, Psychiatric disorders and Renal and urinary disorders (1 each).

[12] More than 1 at-risk PT in some cases.

Information on the BNT162b2 dosage administered to paediatric patients 5 years to less than 12 years was reported as follows:

- Adult dosage/formulation (information was provided in the narrative and/or in the Verbatim as "Adult dose/Adult formulation or Purple/Grey cap" or the dose was 0.3 mL): 23 cases
    - In 9 non-serious cases an Overdose was reported; in 7 cases no additional clinical events were co-reported, while in the 2 remaining cases Pyrexia (2), Erythema, Feeling hot, Lymphadenopathy and Pain (1 each) were co-reported.
    - In 5 cases, of which 2 were serious, clinical events[13] were reported upon administration of the booster dose.
    - In the remaining 9 non-serious cases only at-risk terms indicative of medication errors and/or off-label used were reported with no clinical adverse events.
- Paediatric dosage/formulation (including cases where the adult dosage/formulation was not administered, or information was provided in the narrative and/or in the Verbatim as "Orange cap/Tris" or the dose was reported as 10 micrograms / 0.2 mL): 96 cases
    - In 15 non-serious cases an Overdose was reported as the vaccine was administered either undiluted or with wrong dilution. No additional clinical events were co-reported in these cases.
    - In 36 cases, of which 16 were serious, clinical events[14] were reported upon administration of the booster dose.
    - In the remaining 45 non-serious cases[15] only at-risk terms indicative of medication errors and/or off-label used were reported with no clinical adverse events.

Serious cases of note

Out of the 18 serious cases, 5 cases where the seriousness criterion was reported as Hospitalization Required or Death are summarized below.

- **Fatal case (1 consumer case received through the Regulatory Authority)**

The fatal case, from a non-contactable consumer, refers to a patient in an EU country in the 5- to 11-year-old age group and contains very little information. This child was reported to have received a dose of BNT162b2 as a booster dose (PTs: Off label use, Product administered to patient of inappropriate age), after a primary series from an unknown manufacturer. Dyspnoea occurred 69 days after the booster dose; the child died on an unknown date due to dyspnoea. It was unknown if an autopsy was performed. The report was assessed as Unclassifiable by PEI.

- **Myocarditis (2 Health Care Professional cases received through the Regulatory Authority)**

- A patient in an EU country in the 5- to 11-year-old age group received a dose 3 (0.3 mL) of BNT162b2. Three (3) days later while exercising, the child experienced sudden precordial chest pain associated with breathlessness lasting 30 minutes. The child was hospitalised for myocarditis and several non-serious clinical events (Troponin abnormal, Hyperaemia, Chromaturia, Protein urine present, Urine ketone body present, pH urine increased, Sinus arrhythmia, left ventricular

[13] Including 1 case of Myocarditis and 1 case of Multisystem inflammatory syndrome in children.
[14] Including 1 case with fatal outcome (Off label use, Immunisation, Dyspnoea, Product administered to patient of inappropriate age), 1 case of Myocarditis; 8 cases of Drug ineffective/Vaccination failure and COVID-19/ Suspected COVID-19; 1 case of Guillain-Barre syndrome, 2 cases indicative of swelling (Bone swelling/Parotid gland enlargement and Axillary pain/Swelling), and 1 case each of Lymphadenopathy, Syncope and Pyrexia/Abdominal pain.
[15] There were 4 unlocked serious cases, part of cluster of 5 cases coding the PTs Product administration error, Poor quality product administered; these cases were re-assessed as non-serious cases after the DLP.

hypertrophy, Electrocardiogram abnormal and Blood urine present) were reported. Myocarditis resolved after 1 day. It was also reported but not elaborated on that "a possible minimal myocardial rupture" occurred with onset in the same month of the booster dose, resolved quickly and spontaneously and was thought to be related to sports. Medical history and concomitant medications were not reported.

- A patient in an EU country in the 5- to 11-year-old age group received a booster dose of BNT162b2 21 days after a primary series from an unknown manufacturer. Probable subclinical myocarditis (PT Myocarditis) and Troponin increased were reported on an unknown date; Chest pain with Dyspnoea were reported 10 days after the booster dose and Chest pain and Palpitations were reported 13 days after the booster dose. No other patient detail was provided (ie, diagnostic tests, medical history, concomitant medications, course of the event). The patient recovered at the time of the reporting.

- **Guillain-Barre syndrome (1 consumer case)**

- An individual of unknown gender in an Asian/Pacific country in the 5- to 11-year-old age group received a booster dose (dose number unknown) with BNT162b2 after a primary series from an unknown manufacturer; medical history and concomitant medications were not reported. On an unknown date the child was diagnosed with Guillain-Barré syndrome and was hospitalised. Diagnostic studies and clinical details were not provided and the clinical outcome was unknown.

- **Multisystem inflammatory syndrome in children (1 consumer case received through the Regulatory Authority)**

- A patient in an EU country in the 5- to 11-year-old age group (details on medical history and concomitant medication not provided), received as booster dose 0.3 mL of BNT162b2 after a primary vaccination series from an unknown manufacturer. The same day of the administration of the booster dose, the child developed Multisystem inflammatory syndrome (MIS-C) and was hospitalised; Rash and Pyrexia occurred 23 days after the booster dose. The following non-serious PTs were also reported, with an unknown onset date and clinical outcome: Abdominal pain, Fatigue and Pallor. Rash and pyrexia resolved after treatment with intravenous immune globulin, prednisolone and acetylsalicylic acid. MIS-C was reported as resolved on an unknown date. The report was assessed as Unclassifiable by PEI.

MAH Conclusion

Review of the cumulative available post-marketing data in individuals aged 5 to less than 12 years, did not identify any additional or unexpected risks associated with administration of BNT162b2 and is consistent with the favorable benefit risk balance observed in the clinical study. Post-marketing surveillance activities will continue.

b. Both the number of administered and distributed booster doses and observed AEs should be described and evaluated

It is not possible to discriminate how many doses of the BNT162b2 vaccine paediatric tris-sucrose presentation (10 micrograms/dose) out of 4,331,200 shipped to the US between 17 May 2022 and 22 June 2022 were administered as primary series or as booster doses in individuals aged 5 to less than 12 years.

Considering that up to now BNT162b2 was the only vaccine authorized in the US as a booster in individuals aged 5 to less than 12 years, as per the information available at the US CDC COVID Data

Tracker,[16] it is estimated that 497,632 individuals aged 5 to less than 12 years had received a booster dose of BNT162b2 vaccine in the US as of 22 June 2022. These publicly available data may be more indicative of the actual exposure in persons compared to the shipped doses, however it should be noted that these data may also be incomplete.

Assessment of the MAH's response

In total has 119 post-marketing cases been reported and submitted by the MAH. The majority of the cases fell in the categories Injury, poisoning and procedural complications (160 events), General disorders and administration site conditions (52 events).

Two events of myocarditis have been reported in two children in the 5- to 11-year-old age group, one case developed ten days and the other three days after administration of booster vaccination. For the case reported three days after booster dose laboratory workup (including abnormal troponin) has been presented, however, medical history is missing. The case that occurred 10 days after booster vaccination lacks details of description of medical history and clinical presentations which limits the possibility to assess causality. Both cases resolved. In both cases possible confounding factors cannot be properly excluded limiting firm conclusion on causality. Myocarditis is already described in section 4.4 and 4.8 of the SmPC.

One case of Guillain-Barré has been reported from an Asian/Pacific country, medical history and the exact type of vaccine is unknown. Thus, the case cannot be firmly evaluated.

One case of MIS-C was reported based on a consumer report submitted to the Agency. The case is described as MIS-C that developed the same day as vaccination, no results of clinical or laboratory evaluations have been provided. Therefore, causality cannot be assessed due to the limited information.

Conclusion

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

☒No need to update overall conclusion and impact on benefit-risk balance

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

BNT162b2 10 µg is administered intramuscularly (IM) as a primary series of two doses given 3 weeks apart to individuals ≥5 years of age. According to the present label, booster doses may be administered to severely immunocompromised individuals ≥5 years of age.

This application seeks an extension of the indication to all children 5 to <12 years, for a booster (third) dose of BNT162b2 10-µg.

The application is based on clinical data from Study C4591007 Phase 2/3 demonstrating the safety and tolerability in approximately 400 children. Moreover, data include immune responses from a subset of approximately 130 participants against the SARS-CoV-2 wild-type reference in approximately 130 participants, as well as responses against the Omicron BA1 variant in approximately 30 participants. Follow up is for at least 1-month post-Dose 3 f.

[16] Centers for Disease Control and Prevention (CDC). COVID Data Tracker. Available at: https://covid.cdc.gov/covid-data-tracker/#vaccinations/CDC COVID Data Tracker (accessed: 24 June 2022).

Study C4591007 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 study including healthy children from 6 months to <12 years of age. The dose selection of Phase 1 shows that the suitable dose of Comirnaty for 5 to <12 years is 10-µg.

In Phase 2/3 the participants randomized 2:1 to receive vaccine or placebo, The study was conducted at sites in the US, Finland, Poland, and Spain. The participants could be unblinded to treatment assignment at 6 months after Dose 2.

The protocol specified timing of booster vaccination for participants 5 to <12 years of age was ≥6 months after Dose 2; therefore, booster (third) doses have been administered to participants in this age group in an open-label manner. Participants in the study will continue to be followed in an open-label observational manner until the end of the study which is acceptable.

The basis of inferring BNT162b2 effectiveness in children is immune response data. Immunogenicity data include SARS-CoV-2 neutralizing titers against the wild-type strain and the Omicron BA1. variant after a second dose and booster (third) dose of BNT162b2 10-µg, up to 1-month post-Dose 3. Immunological response after 3 doses vs. 2 doses of Comirnaty was compared. Descriptive analysis of GMTs, GMR and seroresponse in 2 dose group and 3 dose group were presented. No statistical hypothesis of superior or non-inferior immune response was studied.

As the pandemic has evolved, the study population without evidence of previous SARS-COV-2 infection has decreased. In addition, there were not many blood samples available from post-dose 1 and 2. This resulted in a reduced sample size.

Generally, all the immunological results showed that higher neutralising titres are obtained after the third dose compared to after the second dose of Comirnaty 10 µg among children ages 5 to below 12. The GMR for participants with available titers at 1-month post-Dose 3 (N=67) compared to those with available titers at 1-month post-Dose 2 (N=96) was 2.17 (2-sided 95% CI: 1.76, 2.68)).

This is an expected result, given what was previously demonstrated for adults with Comirnaty 30 µg.

Neutralising titres had declined before the third dose compared to 1 month after dose 2, as anticipated. The seroresponse rate was almost 100% after 3rd dose, using pre-dose values as reference. There was one non-responder observed with very low GMT values after the third dose. This is unexpected but is understood as an outlier which does not impact overall conclusions.

A validated SARS-CoV-2 neutralization assay for the SARS-CoV-2 reference strain was used for the primary analysis. However, for the Omicron BA1. variant, an unvalidated assay FFRNT was used, which may affect the robustness of the data obtained. In addition, the samples size was lower than expected for immunogenicity analysis for Omicron variant (N=17). Given study conduct, data are considered descriptive rather than inferential. The immune response associated with a booster (third) dose of BNT162b2 10-µg administered approximately 6 months after the second dose to children 5 to <12 years of age is expected to confer protection against severe COVID-19 including severe disease caused by Omicron.

In conclusion, essentially descriptive data support the assumption based on the boosting of older individuals, of the benefit of a third dose given at approximately 6 months after the primary series, in terms of restoring immunity.

The safety database constitutes of 401 subjects aged 5-<12 years of which a vast majority received their booster dose 8-9 months post dose 2 (87%). Based on this data, the MAH has proposed that the booster dose should be administered at least six months after dose 2, which is the recommended dose interval described in section 4.2 of the SmPC and considered acceptable.

None of the participants were excluded from the safety population for other reasons. Local and systemic reactogenicity was recorded for 7 days after each dose administration using an electronic diary (e-diary). AEs were collected from Dose 3 to 1 month after Dose 3 and serious AEs (SAEs) are collected from Dose 3 to 6 months after Dose 3.

Duration of follow up was 1-2 months for all 401 subjects. Reactogenicity data after dose 3 is available for 371 subjects. It is noted that a significant lower number of subjects reported solicited events in the e-diary system, however, at least 75% of the subjects reported in the e-diary from day 2 and onwards.

Reactogenicity profile was in line with had been observed for primary series in this population. The most common local reaction was pain at injection site (74%). Most of the local reactions were mild to moderate in intensity. Fatigue (46%), followed by headache (34%) was the most commonly reported systemic reaction after dose 3.

Antipyretic pain medication was used by 31%, which is a higher frequency compared to dose 2 (22%) and dose 1 (13%) The frequency of fever was not higher after dose 3 (9% dose 2; 7% dose 3), but a slightly increase of reported headache (30% dose 2; 34% dose 3) and muscle pain (13% dose 2; 18% dose 3) might explain the increased use of antipyretic pain medication

AEs were covered for a median of 1.3 months post-dose 3. The AE profile is overall acceptable and consistent with the known side effect profile of Comirnaty and belonged especially to the SOCs "General disorders and administration site conditions" (2.2%), "Gastrointestinal disorders" (1.5%), "Nervous system disorders" (1.0%) and "Musculoskeletal and connective tissue disorders" (0.5%). Notably, lymphadenopathy was reported in 10 participants (2.5%, a higher frequency than observed after dose 2 (0.9%)), and rash (not related to study product) in 1 participant (0.2%). No immediate AEs were reported within 30 minutes of receiving Dose 3 of BNT162b2 10 µg. No SAEs, life threatening events or deaths were reported. One severe AE (pyrexia of 39.0C in a participant in the 5 to 11 years old age group) was reported one day post-dose 3, which resolved within 3 days.

It is noted that FDA has recently approved a booster dose for children aged 5-<12 years, and the MAH has submitted available post-marketing safety data in relation to the use of a booster dose in this population.

Overall, the side effect profile after booster dose is consistent with the safety profile known for primary series of Comirnaty 10 µg administered to individuals aged 5-<12 years of age.

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 and IIIB

Update of sections 4.2, 4.8 and 5.1 of the SmPC of COMIRNATY 10 µg Concentrate for dispersion for injection in order to introduce a booster dose for children 5 to 11 years of age based on interim results from study C4591007; this is a Phase 1, Open-Label Dose-Finding Study to Evaluate Safety, Tolerability, and Immunogenicity and Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate Against COVID-19 in Healthy Children and Young Adults; the Package Leaflet is 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 Annex(es) I and IIIB are recommended.

[i] Zou J, Xia H, Xie X, et al. Neutralization against Omicron SARS-CoV-2 from previous non-Omicron infection. Nat Commun 2022;13:852;[ePub]doi:10.1038/s41467-022-28544-w

[ii] Kurhade C, Zou J, Xia H, et al. Neutralization of Omicron BA.1, BA.2, and BA.3 SARS-CoV-2 by 3 doses of BNT162b2 vaccine. bioRxiv 2022;[ePub] doi:10.1101/2022.03.24.485633

[iii] Liu Y, Liu J, Xia H, et al. Neutralizing activity of BNT162b2-elicited serum. N Engl J Med 2021;384:1466-8.

[iv] Muruato AE, Fontes-Garfias CR, Ren P, et al. A high-throughput neutralizing antibody assay for COVID-19 diagnosis and vaccine evaluation. Nat Commun 2020;11:4059.

[v] Kurhade C, Zou J, Xia H, et al. Neutralization of Omnicron sublineages and Delatcron SARS-CoV-2 by 3 doses of BNT162b2 vaccine or BA.1 infection. bioRxiv. 2022. DOI: https://doi.org/10.1101/2022.06.05.494889.