Application Type	BLA Supplement
STN	125742/656
CBER Received Date	March 18, 2025
PDUFA Goal Date	January 16, 2026
Division / Office	(b) (6) /OVRR
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
Priority Review	No
Reviewer Name(s)	(b) (6) (b) (6)
Review Completion Date / Stamped Date	
Concurrence	(b) (6) Concurring Reviewer, (b) (6)
	(b) (6) (b) (6) , (b) (6)
Applicant	Pfizer, Inc for BioNTech Manufacturing GmbH
Established Name	COVID-19 Vaccine, mRNA
Trade Name	COMIRNATY
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	One dose of 10 micrograms of COVID-19 mRNA Vaccine, embeded in lipid nanoparticles
Dosage Form(s) and Route(s) of Administration	Single-dose vial contains 10 µg of COVID-19 mRNA in 0.3 mL injection volume, Intramuscular
Dosing Regimen	Single-dose of 0.3 mL
Indication(s) and Intended Population(s)	Active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 65 years of age and older, or individuals 5 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

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1. Executive Summary

Biologics License Application (BLA) 125742 for the mRNA COVID-19 Vaccine (BNT162b2, or COMIRNATY) was approved in the U.S. on August 23, 2021 for active immunization to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. On July 8, 2022, FDA approved the sBLA to extend licensure of COMIRNATY to adolescents 12 through 15 years of age. On August 22, 2024, FDA approved the sBLA to include use of COMIRNATY as a single dose for individuals 12 years of age and older for the 2024-2025 Formula.

Based on the New England Journal of Medicine article entitled "An Evidence-Based Approach to Covid-19 Vaccination", published by the Commissioner and the CBER Center Director, on June 6, 2025, CBER requested the applicant to update the United States Prescribing Information (USPI) to limit the indicated population to 65 years of age and older, or 5 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. In addition, CBER requested concept sheet/protocols for three post marketing commitment (PMC) clinical studies: 1) Prospectively designed study to evaluate safety and immunogenicity of COMIRNATY (2025-2026 Formula) in participants 65 years of age and older, and 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19; 2) A randomized, double-blind, saline placebo-controlled study to evaluate the efficacy and safety of COMIRNATY in individuals 50 through 64 years of age without underlying condition that puts them at high risk for severe outcomes from COVID-19; 3) Prospectively designed study to evaluate safety and immunogenicity of COMIRNATY (2025-2026 Formula) in participants 5 years through 11 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

The applicant, BioNTech and Pfizer, submitted this supplemental BLA (sBLA), STN 125742/656, for COMIRNATY to (1) expand the indication to children 5 to 11 years of age with a 10-mcg single dose; (2) update the vaccine to the 2025-2026 formulation; and (3) add information to the USPI on the concomitant administration of Respiratory Syncytial Virus (RSV) stabilized prefusion F subunit vaccine (RSVpreF or ABRYSVO) and Pfizer's bivalent COVID-19 vaccine (BNT162b2 encoding for the original strain and Omicron BA.4/BA.5), with and without high-dose quadrivalent influenza vaccine (QIV) in individuals 65 years and older.

Please refer to (b) (6) memo for the statistical review of Study C5481001 Substudy A (SSA) regarding the co-administration of the RSV and Pfizer's bivalent COVID-19 vaccine, with and without high-dose QIV in individuals 65 years and older. This statistical review memo focuses on clinical data supporting the expansion of the indication as well as the concept sheets for the aforementioned PMC clinical studies. Specifically, the clinical data supporting the expansion of indication include 1) efficacy and safety data from vaccine-naïve participants 5 to <12 years of age in Study C4591007 following administration of a two dose series of the original monovalent BNT162b2 (10

μg), followed by a third dose of monovalent BNT162b2 (10 μg); and 2) immunogenicity and safety data in vaccine-naïve participants 5 to <12 years of age in C4591048 Substudy E (SSE) following administration of a single dose of BNT162b2 (Omi XBB.1.5) at 10 μg.

C4591007

Study C4591007 was a Phase 1/2/3 study to initially evaluate up to three dose levels of BNT162b2 in up to three age groups (5 to <12 years, 2 to <5 years, and 6 months to <2 years of age) for safety, immunogenicity, and efficacy. The Phase 2/3 portion of the study evaluated the selected dose level from Phase 1 dose-finding in each age group, including a total of approximately 4500 participants 5 to <12 years of age. Participants were randomized in a 2:1 ratio to receive the original monovalent BNT162b2 (10 μg) or placebo as a 2-dose series, given 21 days apart. A third dose of original BNT162b2 was administered at least 5 months after the second dose in an open-label fashion.

In the evaluable efficacy (2-dose) population without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2 (n = ~4000), the observed vaccine efficacy (VE) among 5 to <12 years of age was 88.2% (2-sided 95% CI: 76.2%, 94.7%) for first COVID-19 cases confirmed from ≥7 days after Dose 2 to before Dose 3 through the blinded follow-up period, meeting the predefined success criterion as the lower limit of the 95% CI for VE was >30%. A descriptive analysis of VE in participants 5 years through 11 years of age with at least one comorbidity of interest without evidence of prior SARS-CoV-2 infection was 92.3% (2-sided 95% CI: 66.0%, 99.2%).

The safety population for the analysis of the 2-dose series of BNT162b2 consisted of 3109 participants in the BNT162b2 group and 1538 participants in the placebo group. In both BNT162b2 (10 μg) and placebo groups, pain at the injection site was the most frequently reported local reaction (72.9% and 31.5% after Dose 1, in the BNT162b2 and placebo groups, respectively; 71.2% and 28.5% after Dose 2, in the BNT162b2 and placebo groups, respectively). In the BNT162b2 group, most systemic events were reported at higher frequencies and severity after Dose 2 compared to after Dose 1, with the exceptions of vomiting and diarrhea, both of which were reported infrequently and at similar frequencies after each dose. After Dose 2, most systemic events were reported less frequently in the placebo group compared with the BNT162b2 group. Overall, the numbers of participants reporting any adverse events (AEs) from Dose 1 to 1 month after Dose 2 were similar in the BNT162b2 (10.7%) and placebo (9.8%) groups. Any related AEs and any serious adverse events (SAEs) were reported in the BNT162b2 and placebo groups by ≤3.5%, and 0.1%, respectively. There were no cases of myocarditis/pericarditis or deaths reported in the study as of the data cutoff date (February 28, 2023).

C4591048

C4591048 was a Phase 1/2/3 master protocol to investigate the safety, tolerability, and immunogenicity of variant-adapted BNT162b2 RNA-based vaccine candidates in healthy children. C4591048 SSE was a Phase 2/3 open-label study to evaluate the safety, tolerability, and immunogenicity of a single 10-μg dose of BNT162b2 (Omi XBB.1.5) in

participants 5 to <12 years of age who were COVID-19 vaccine–naïve. Approximately 300 participants 5 to <12 years of age were enrolled in Substudy E.

In the evaluable immunogenicity population, model-based geometric mean ratio (GMR) of Omicron XBB.1.5-neutralizing titers for the BNT162b2 (Omi XBB.1.5) 10-µg group in C4591048 SSE (n=285) to vaccine-experienced participants ≥12 years of age who received a single 30-µg dose of BNT162b2 (Omi XBB.1.5) in C4591054 Substudy A (n=302) was 1.81 (2-sided 95% CI: 1.51, 2.16). The adjusted difference in percentages of participants with seroresponse between the BNT162b2 (Omi XBB.1.5) 10-µg group and BNT162b2 (Omi XBB.1.5) 30-µg group was 8.97% (95% CI: 3.91%, 14.02%), where seroresponse is defined as achieving a ≥4-fold rise from baseline. The immunobridging success criteria were met since the lower limit of the 2-sided 95% CI was greater than 0.67and the point estimate was ≥0.8 for GMR, and the lower limit of the 2-sided 95% CI for the adjusted difference in percentages of participants with seroresponse was >-10%.

Pain at the injection site was the most frequently reported local reaction within 7 days after study vaccination (43%). Fatigue, headache, and muscle pain were the most frequently reported (range: 10%-15%) systemic events within 7 days after study vaccination. Eleven participants (3.5%) reported AEs from the study vaccination through 1 month after the study vaccination. Three participants (1%) reported SAEs from study vaccination through 6 months after study vaccination, of which one (seizure) was considered to be related to study vaccination by the investigator. There were no cases of myocarditis/pericarditis or deaths reported from study vaccination through 6 months after study vaccination.

Conclusion
Study C4591007 met the success criteria for the secondary efficacy endpoint. Study C4591048 SSE met the success criteria for the primary immunogenicity endpoints. I defer to the clinical reviewer on the safety assessment of this vaccine as well as the regulatory action for this sBLA.

2. CLINICAL AND REGULATORY BACKGROUND

In light of the Vaccines and Related Biological Products (VRBPAC) meeting regarding the SARS-CoV-2 strain composition for the 2025-2026 Formula for COVID-19 vaccines, CBER recommended on May 22, 2025, that the applicant develop a monovalent JN.1 COVID-19 vaccine for age-appropriate use in potentially eligible populations. The preferred JN.1-lineage for the COVID-19 vaccines (2025-2026 Formula) is the LP.8.1 strain ("FDA Advice on 2025-2026 Formula for COVID-19 vaccines"). Based on the May 20, 2025 New England Journal of Medicine article entitled "An Evidence-Based Approach to Covid-19 Vaccination", published by the Commissioner and the CBER Center Director, on May 27, 2025, CBER sent an advice addendum to request that the applicant submit an "Efficacy Prior Approval Supplement" to the original BLA 125742 with an updated United States Prescribing Information (USPI) with the following indication:
COMIRNATY is approved for use in individuals who are:

- 65 years of age and older, or

- 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

In addition, CBER requested that the applicant submit concept sheets/protocols for the first two PMC clinical studies mentioned in Section 1.

Accordingly, on June 6, 2025, CBER requested the applicant to update the USPI seeking under the current supplement (sBLA 125742/656) as:
COMIRNATY is approved for use in individuals who are:

- 65 years of age and older, or
- 5 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

CBER also requested an additional concept sheet/protocol for a PMC clinical study in individuals 5 through 11 years of age (last PMC clinical study mentioned in Section 1).

In accordance with the FDA advice on 2025-2026 Formula for COVID-19 vaccines, the advice addendum and the information request (IR) dated June 6, 2025, the applicant submitted the information (proposed revised labeling, concept sheets for three PMC clinical studies, etc.) to STN 125742/696.

On July 11, 2025, CBER requested the applicant to consolidate supplements STN 125742/696, STN 125742/656 and STN 125742/634 to streamline the review process and to support combined labeling. STN 125742/634 contains information for concomitant administration of COMIRNATY with RSV vaccines in individuals ≥18 years of age, with and without high dose flu vaccine in individuals ≥65 years of age. In response to CBER's request, the applicant submitted all the information that was previously submitted to STN 125742/696 to STN 125742/656.21 and submitted all the information that was previously submitted to STN 125742/634 to STN 125742/656.22.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The quality of the submission was sufficient for a statistical evaluation.

3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issues were identified.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

I defer to reviewers from other disciplines.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Multiple interim clinical study reports (CSR) for Study C4591007 were submitted to the sBLA. Specifically, the 1-month post-dose 2 (1MPD2) and 1-month-post dose-3 (1MPD3) interim reports for 5 to <12 years of age included immunogenicity results after the primary series and after a third (booster) dose, respectively, that had been reviewed under EUA 27034.324 and EUA 27034.528, and hence are not re-reviewed in this sBLA. This statistical review memo focuses on the relevant clinical data that have not been reviewed previously, including 1) the efficacy and safety data from vaccine-naïve participants 5 to <12 years of age in Study C4591007 following administration of a two dose series of the original monovalent BNT162b2 (10 μg); 2) immunogenicity and safety data in vaccine-naïve participants 5 to <12 years of age in C4591048 substudy E (SSE) following administration of a single dose of BNT162b2 (Omi XBB.1.5) at 10 μg; and 3) concept sheets for the aforementioned PMC clinical studies.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following submissions were reviewed:

- STN 125742/656.0 Module 2.5 Clinical Overview
- STN 125742/656.0 Module 2.7 Clinical Summary
- STN 125742/656.0 Module 5 Clinical Study Reports
- STN 125742/656.4 Module 1.11 Information Not Covered Under Modules 2 to 5
- STN 125742/656.9 Module 1.11 Information Not Covered Under Modules 2 to 5
- STN 125742/656.0, STN 125742/656.11, STN 125742/656.19, STN 125742/656.20 Module 1.14 Labeling
- STN 125742/656.12 Module 1.11 Information Not Covered Under Modules 2 to 5
- STN 125742/656.21 Module 2.3 Quality Overall Summary

5.3 Table of Studies/Clinical Trials

Table 1 displays an overview of the clinical trials providing efficacy, immunogenicity, and safety data to support this application.

Table 1. Overview of Clinical Trials

Protocol No.	**Study Design**	**No. of Subjects (By Treatment Group)**	**Number of Sites, Location Study Status**
C4591007, Phase 2/3, 5 to <12 Years of Age	placebo-controlled, randomized, double-blinded, multicenter	approximately 4500 participants 5 to <12 years of age, randomized in a 2:1 ratio to receive original monovalent BNT162b2 (10 μg) or placebo	eighty-six sites in the United States, Spain, Poland and Finland first participant first visit (FPFV): March 24, 2021 last participant last visit (LPLV): December 8, 2023
C4591048 SSD	open-label	136 participants enrolled to receive a third or fourth dose with bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 μg in participants 5 to <12 years of age	ten sites in the United States FPFV: September 23, 2022 LPLV: August 17, 2023
C4591048 SSE	open-label	approximately 300 COVID-19 vaccine-naïve participants who were 5 to <12 years of age were enrolled to receive a single dose of BNT162b2 (Omi XBB.1.5) 10-μg	thirty sites in the U.S., South Africa, and Brazil FPFV: October 31, 2023 LPLV: October 10, 2024

Source: Information based on Module 2.5 Clinical Overview submitted to BLA 125742/656.0.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: C4591007

A Phase 1, Open-Label Dose-Finding Study to Evaluate Safety, Tolerability, and Immunogenicity and A 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

Multiple interim clinical study reports (CSR) for Study C4591007 were submitted to the sBLA. This memo focuses on the review of the Phase 2/3 data for children 5 to <12 years of age contained in two interim CSRs: 6-Month Post-Dose 2 interim CSR for children 5 to <12 years of age, and 6-Month Post-Dose 3 interim CSR for children 6 Months to <12 years of age. Specifically, Phase 2/3 safety and efficacy data for children 5 to <12 years of age up to 6-Month Post-Dose 2 and safety data for children 5 to <12 years of age up to 6-Month Post-Dose 3 are reviewed.

6.1.1 Objectives

Safety Objective:

- To define the safety profile of BNT162b2 in all participants in Phase 2/3 in children 5 to <12 years of age.

Primary Immunogenicity Objective:

- To immunobridge the immune response elicited by prophylactic BNT162b2 between Phase 2/3 participants at the dose selected in each age group and participants 16 to 25 years of age from the C4591001 study without serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection.

Secondary Objective:

- To evaluate the efficacy of BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 to prior to Dose 3 during the blinded follow-up period in children 5 to <12 years of age.
- To describe the immune responses elicited by prophylactic BNT162b2 at the dose level selected in each age group and persistence of immune response in Phase 2/3 participants without serological or virological evidence of past SARS-CoV-2 infection.

Reviewer's Comment:
The results for the primary and secondary immunogenicity objectives were summarized in the 1MPD2 and 1MPD3 interim reports, respectively, and were used to support the Emergency Use Authorization (EUA) of the primary series and booster dose of BNT162b2 in individuals 5 to <12 years of age. These immunogenicity results were reviewed under EUA 27034.324 and 27034.528 and are not re-reviewed in this memo.

6.1.2 Design Overview

For the 5 to <12 years of age group in Study C4591007, the Phase 1 portion tested dose levels of 10, 20, and 30 µg BNT162b2, administered as a 2-dose series, 21 days apart, with 16 participants enrolled into each dose group. The selected dose for this age group (10 µg BNT162b2) was administered as a 2-dose series, 21 days apart in Phase 2/3 to approximately 4500 participants who were randomized 2:1 to receive BNT162b2 (10 µg) or placebo. Protocol Amendment 6 added a booster (third) dose at the selected dose level, which was administered at least 5 months after the second dose in an open-label fashion. Unblinding was completed prior to the 6-month post-Dose 2 study visit after the FDA issued an EUA (dated October 29, 2021) in the U.S. Participants who received placebo after the initial randomization received BNT162b2 after unblinding.

6.1.3 Population

The study enrolled approximately 4500 healthy children 5 to <12 years of age.

6.1.4 Study Treatments or Agents Mandated by the Protocol

BNT162b2 (or placebo) was administered intramuscularly (IM) at a dose of 10 µg into the deltoid muscle. The placebo was normal saline, 0.9% sodium chloride solution.

6.1.6 Sites and Centers

Eighty-six sites in the United States, Spain, Poland and Finland.

6.1.7 Surveillance/Monitoring

Please refer to clinical reviewer's memo.

6.1.8 Endpoints and Criteria for Study Success

Safety Endpoints:

- Local reactions for up to 7 days following each dose
- Systemic events for up to 7 days following each dose
- AEs from Dose 1 to 1 month after Dose 2 and from Dose 3 to 1 month after Dose 3
- SAEs from Dose 1 to 6 months after Dose 2 and from Dose 3 to 6 months after Dose 3

Secondary Endpoint (Efficacy):

- Confirmed COVID-19 incidence from 7 days after Dose 2 to prior to Dose 3 per 1000 person-years of blinded follow-up

The assessment of vaccine efficacy (VE) was based on testing the following hypothesis: H_0: VE $\leq$30% vs H_1: VE >30%.

Reviewer's Comments:
1. The immunobridging hypotheses would be tested first for the primary immunogenicity objective for participants 5 to <12 years of age and the hypothesis for the secondary efficacy endpoint would only be assessed if immunobridging for the primary endpoint is successful and if at least 21 cases are accrued, per the protocol. According to 1-Month Post-Dose 2 interim CSR, immunobridging success criteria were met for the 5 to <12 years of age group and the required number (21) of confirmed COVID-19 cases was accrued; therefore, the secondary VE objective was assessed and presented in the current submission.
2. Confirmed COVID-19 case was defined as a positive nucleic acid amplification-based test (NAAT) AND presence of at least 1 of the following symptoms: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea, as defined by ≥3 loose stools per day; vomiting. The positive SARS-CoV-2 NAAT needs to be during, or within 4 days before or after the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test), which would trigger a potential COVID-19 illness visit.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis populations
The safety population contained all subjects who entered the study and received one vaccination. Participants were summarized by vaccine group according to the study interventions they actually received. The evaluable efficacy (2-dose) population included all eligible randomized participants who received two doses of the vaccine to which they were randomized within the predefined window and had no other important protocol

deviations as determined by the clinician. The evaluable efficacy population was the primary analysis population for the efficacy analysis.

Secondary efficacy analysis

VE was estimated as 100 × (1 – IRR), where IRR is the incidence rate ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after Dose 2 to prior to Dose 3 during the blinded follow-up period. VE and the associated 2-sided 95% CI were derived using the Clopper-Pearson method adjusted for surveillance time. VE among participants without evidence of infection, and regardless of infection status (prior to 7 days after receipt of Dose 2) were tested sequentially in the order as stated.

Safety endpoints were summarized descriptively.

Sample size determination

Since it required at least 21 cases to achieve 77.0% power to conclude true VE >30% with the assumption of a true VE of 80%, hypothesis testing would be conducted only if at least 21 cases were accrued and immunobridging before the primary endpoint was successful. With the same assumptions, 33 cases would provide ~93.8% power.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The analysis population of participants 5 to <12 years of age prior to Dose 3 or unblinding in Phase 2/3 is summarized in Table 2. In total, 3108 participants were randomized to receive BNT162b2 (10 μg) and 1539 participants were randomized to receive placebo. One participant, who was randomized to the placebo group, received two doses of BNT162b2. The evaluable efficacy (2-dose) population for the Phase 2/3 blinded follow-up period included 3018 participants and 1511 participants in the BNT162b2 and placebo groups, respectively. Ninety participants (2.9%) in the BNT162b2 group and 28 participants (1.8%) in the placebo group were excluded from the evaluable efficacy (2-dose) population. The reasons for exclusion include: did not receive 2 vaccinations as randomized prior to unblinding; did not receive Dose 2 within the predefined window (19-42 days after Dose 1); had other important protocol deviations on or prior to 7 days after Dose 2. The proportions of participants without evidence of infection prior to 7 days after Dose 2 were balanced: 87.0% (BNT162b2) versus 87.6% (placebo), in the two groups.

Table 2. Analysis Populations in Study C4591007 (6-Month Post-Dose 2)

	BNT162b2	**Placebo**	**Total**
	n (%)	n (%)	n (%)
Safety population	3109 (100.0)	1538 (100.0)	4647 (100.0)
Evaluable efficacy (2-dose) population	3018 (97.1)	1511 (98.2)	4529 (97.5)
Participants without evidence of infection prior to 7 days after Dose 2	2703 (87.0)	1348 (87.6)	4051 (87.2)

Source: Adapted from Tables 8 and 11 in the 6-Month Post-Dose 2 interim CSR for Study C4591007.

Fourteen (14) participants (0.5%) in the BNT162b2 group and 12 participants (0.8%) in the placebo group withdrew from the study at some point after Dose 1 and before Dose 3 or unblinding. None of these withdrawals were reported as due to an AE; most (18/26) were withdrawn by parent or guardian.

Demographic characteristics for Phase 2/3 participants 5 to <12 years of age were similar in BNT162b2 and placebo groups in the safety population (Table 3). Most participants were White (77.5%). The median age was 8.0 years and 51.4% of participants were male. Similar proportions of participants in the BNT162b2 group (9.5%) and placebo group (9.6%) were baseline SARS-CoV-2 positive. In the safety population, 26.7% of participants in the BNT162b2 group and 26.9% of participants in the placebo group had one or more comorbidities that increase the risk of severe COVID-19 disease, defined as participants who had at least one of the pre-specified comorbidities based on MMWR Morb Mortal Wkly Rep. 2020;69(32):1081-8 and/or obesity (BMI $\geq 95^{th}$ percentile).

Demographics of participants in the evaluable efficacy population were similar in the BNT162b2 and placebo groups, which were similar compared to the overall safety population.

A total of 2408 subjects received three doses of BNT162b2 (10 µg). The safety population for the analysis of three doses of BNT162b2 (10 µg) included 2408 participants. No participants were further excluded from the safety population. Demographics of participants for this population were similar to the safety population who received two doses of BNT162b2.

Table 3. Demographics and Baseline Characteristics in the Safety Population in Study C4591007 (6-Month Post-Dose 2 in Phase 2/3, 5 to <12 Years of Age)

	BNT162b2 (10 µg) N=3109	**Placebo N=1538**	**Total N=4647**
Age (years)			
Mean (std)	8.0 (1.96)	8.0 (1.97)	8.0 (1.96)
Median	8.0	8.0	8.0
Min, Max	5, 11	5, 11	5, 11
Sex n (%)			
Female	1500 (48.2)	759 (49.3)	2251 (54.7)
Male	1609 (51.8)	779 (50.7)	1864 (45.3)
Race n (%)			
White	2402 (77.3)	1199 (78.0)	3601 (77.5)
Black or African American	179 (5.8)	101 (6.6)	280 (6.0)
Asian	258 (8.3)	120 (7.8)	378 (8.1)
American Indian or Alaska Native	13 (0.4)	4 (0.3)	17 (0.4)
Native Hawaiian or other Pacific Islander	10 (0.3)	0	10 (0.2)
Multiracial	235 (7.6)	103 (6.7)	338 (7.3)
Not reported	12 (0.4)	11 (0.7)	23 (0.5)
Baseline SARS-CoV-2 status			
Positive	296 (9.5)	148 (9.6)	444 (9.6)
Negative	2811 (90.4)	1390 (90.4)	4201 (90.4)
Missing	2 (0.1)	0	2 (0.0)
Comorbidities			
Yes	829 (26.7)	414 (26.9)	1243 (26.7)
No	2280 (73.3)	1124 (73.1)	3404 (73.3)

Source: Adapted from Table 12 in the 6-Month Post-Dose 2 interim CSR for Study C4591007.

6.1.11 Efficacy and Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoints

The primary immunogenicity analysis for participants 5 to <12 years of age were reviewed under EUA and are not re-reviewed in this memo.

6.1.11.2 Analyses of Secondary Endpoints

The VE hypothesis for participants 5 to <12 years of age was first evaluated in participants without evidence of prior SARS-CoV-2 infection. In the evaluable efficacy (2-dose) population without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, the observed VE was 88.2% (2-sided 95% CI: 76.2%, 94.7%) for first COVID-19 cases confirmed from 7 days after Dose 2 to before Dose 3 through the blinded follow-up period (Table 4). The predefined success criterion of lower limit of the 95% CI for VE >30% was met.

Table 4. Vaccine Efficacy Among Participants 5 to <12 Years of Age Without Evidence of Infection Prior to 7 Days After Dose 2 in Blinded Follow-Up Period

	BNT162b2 N[a]=2703		**Placebo N[a]=1348**		
	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%) (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2 to before Dose 3	10	0.591 (2640)	42	0.292 (1309)	88.2 (76.2, 94.7)

Source: Adapted from Table 14 in the 6-Month Post-Dose 2 interim CSR for Study C4591007.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

In the evaluable efficacy (2-dose) population with or without evidence of SARS CoV-2 infection prior to 7 days after Dose 2, the observed VE was 85.7% (2-sided 95% CI: 72.4%, 93.2%) for first COVID-19 cases confirmed from 7 days after Dose 2 to before Dose 3 through the blinded follow-up period (Table 5), meeting the success criterion since the lower limit of the 95% CI for VE was >30%. Compared to participants without evidence of prior infection, there were two additional cases of COVID-19 among those with or without evidence of prior infection (both in the BNT162b2 group).

Table 5. Vaccine Efficacy Among Participants 5 to <12 Years of Age With or Without Evidence of Infection Prior to 7 Days After Dose 2 in Blinded Follow-Up Period

	BNT162b2 N[a]= 3018		**Placebo N[a]=1511**		
	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%) (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2 to before Dose 3	12	0.653 (2926)	42	0.326 (1458)	85.7 (72.4, 93.2)

Source: Adapted from Table 15 in the 6-Month Post-Dose 2 interim CSR for Study C4591007.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Reviewer's Comment:
The CDISC datasets for six months post Dose 2 submitted to STN 125742/656.0 were not complete. Specifically, one SDTM dataset "face.xpt" and two ADAM datasets "adfacevd.xpt" and "adfaxcvd.xpt" were truncated. These datasets were the critical

components to verify the primary safety and secondary efficacy analysis results six months post Dose 2 and an IR was issued. In the IR response, the applicant explained that truncation of the observations could be due to the large size of the datasets, and unobserved interruption, such as network fluctuation at the time of loading these datasets for submission build. The applicant also re-submitted the three datasets with complete data to STN 125742/656.4. I was able to verify the primary safety and secondary efficacy analysis results six months post Dose 2 using the updated datasets.

6.1.11.3 Subpopulation Analyses

Vaccine efficacy was not meaningfully different by sex, race, ethnicity, country, or comorbidity status. The subgroup analysis by comorbidity status in participants 5 years through 11 years of age without evidence of prior SARS-CoV-2 infection is presented in Table 6. The vaccine efficacy by comorbidity status is similar to the overall VE of 88.2%.

Table 6. Vaccine Efficacy by Comorbidity Status Among Participants 5 to <12 Years of Age Without Evidence of Infection Prior to 7 Days After Dose 2 in Blinded Follow-Up Period

Participants with at least one comorbidity of interest	**BNT162b2 (10 µg) (N[a]=2703) Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo (N[a]=1348) Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy (%) (95% CI[e])**
Yes	2 0.150 (676)	13 0.075 (336)	92.3 (66.0, 99.2)
No	8 0.441 (1964)	29 0.217 (973)	86.4 (69.5, 94.6)

Source: Adapted from Table 14.15 in the 6-Month Post-Dose 2 interim CSR for Study C4591007.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

6.1.12 Safety Analyses

Table 7 and Table 8 present the frequencies and severity of solicited local and systemic reactions, respectively, within 7 days following Dose 1 or Dose 2.

Local events were reported less frequently in the placebo group compared to the BNT162b2 group after each dose. Pain at the injection site was the most frequently reported local reaction, and the frequency was similar after Dose 1 and after Dose 2 of BNT162b2 (72.9% vs 71.2%). The mean duration of pain at the injection site after Dose 2 was 2.3 days (range 1 to 37 days), for redness 2.0 days (range 1 to 10 days), and for swelling 2.2 days (range 1 to 16 days) in the BNT162b2 group in the blinded placebo-controlled follow-up period. After the first and second dose, most local reactions were

mild or moderate in severity. Severe local reactions were reported infrequently (≤0.2%) in the BNT162b2 and placebo groups after either dose. No Grade 4 local reactions were reported in either group.

Table 7. Frequency and Percentages of Participants With Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Safety Population

	BNT162b2 (10 µg) Dose 1 N[a]=3096 n[b] (%)	Placebo Dose 1 N[a]=1531 to 1532 n[b] (%)	BNT162b2 (10 µg) Dose 2 N[a]=3064 n[b] (%)	Placebo Dose 2 N[a]=1521 to 1522 n[b] (%)
Redness[c]				
Any (≥0.5 cm)	434 (14.0)	91 (5.9)	575 (18.8)	79 (5.2)
Mild	287 (9.3)	78 (5.1)	315 (10.3)	57 (3.7)
Moderate	146 (4.7)	11 (0.7)	257 (8.4)	20 (1.3)
Severe	1 (0.0)	2 (0.1)	3 (0.1)	2 (0.1)
Swelling[c]				
Any (≥0.5 cm)	320 (10.3)	46 (3.0)	450 (14.7)	41 (2.7)
Mild	177 (5.7)	28 (1.8)	247 (8.1)	30 (2.0)
Moderate	142 (4.6)	18 (1.2)	203 (6.6)	11 (0.7)
Severe	1 (0.0)	0	0	0
Pain at the injection site[d]				
Any	2258 (72.9)	482 (31.5)	2181 (71.2)	434 (28.5)
Mild	1810 (58.5)	434 (28.3)	1642 (53.6)	389 (25.6)
Moderate	442 (14.3)	48 (3.1)	533 (17.4)	44 (2.9)
Severe	6 (0.2)	0	6 (0.2)	1 (0.1)

Source: Adapted from Table 14.28 in the 6-Month Post-Dose 2 interim CSR for Study C4591007.
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 reaction.
c. Mild: ≥0.5 to <2.0 cm; Moderate: >2.0 to <7.0 cm; Severe: >7.0 cm.
d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Most systemic events were reported less frequently in the placebo group compared to the BNT162b2 group. Fatigue was the most frequently reported systemic reaction, and the frequency was slightly higher after Dose 2 of BNT162b2 than after Dose 1 (39.2% vs 34.5%). After the first and second dose, most systemic events were mild or moderate in severity. Severe systemic events were infrequent, reported at low incidences (≤0.9%) across BNT162b2 and placebo groups after either dose. In the BNT162b2 group, severe systemic events reported most frequently after Dose 1 and Dose 2 were fatigue (0.2% and 0.9%) and fever (0.1% and 0.7%).

Table 8. Frequency and Percentages of Participants With Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Safety Population

	BNT162b2 Dose 1 N[a]=3096 n[b] (%)	Placebo Dose 1 N[a]=1531 to 1532 n[b] (%)	BNT162b2 Dose 2 N[a]=3064 n[b] (%)	Placebo Dose 2 N[a]=1521 to 1522 n[b] (%)
Fever				
≥38.0°C	64 (2.1)	21 (1.4)	193 (6.3)	21 (1.4)
≥38.0°C to 38.4°C	37 (1.2)	10 (0.7)	101 (3.3)	13 (0.9)
>38.4°C to 38.9°C	22 (0.7)	9 (0.6)	70 (2.3)	5 (0.3)
>38.9°C to 40.0°C	4 (0.1)	2 (0.1)	21 (0.7)	3 (0.2)
>40.0°C	1 (0.0)	0	1 (0.0)	0
Fatigue[c]				
Any	1067 (34.5)	496 (32.4)	1200 (39.2)	383 (25.2)
Mild	702 (22.7)	323 (21.1)	665 (21.7)	230 (15.1)
Moderate	360 (11.6)	171 (11.2)	508 (16.6)	149 (9.8)
Severe	5 (0.2)	2 (0.1)	27 (0.9)	4 (0.3)
Headache[c]				
Any	703 (22.7)	372 (24.3)	870 (28.4)	284 (18.7)
Mild	530 (17.1)	275 (18.0)	576 (18.8)	201 (13.2)
Moderate	170 (5.5)	91 (5.9)	286 (9.3)	82 (5.4)
Severe	3 (0.1)	6 (0.4)	8 (0.3)	1 (0.1)
Chills[c]				
Any	174 (5.6)	84 (5.5)	301 (9.8)	66 (4.3)
Mild	138 (4.5)	69 (4.5)	205 (6.7)	52 (3.4)
Moderate	36 (1.2)	15 (1.0)	94 (3.1)	13 (0.9)
Severe	0	0	2 (0.1)	1 (0.1)
Vomiting[d]				
Any	63 (2.0)	30 (2.0)	62 (2.0)	27 (1.8)
Mild	52 (1.7)	28 (1.8)	56 (1.8)	22 (1.4)
Moderate	11 (0.4)	2 (0.1)	5 (0.2)	5 (0.3)
Severe	0	0	1 (0.0)	0
Diarrhea[e]				
Any	198 (6.4)	75 (4.9)	166 (5.4)	76 (5.0)
Mild	184 (5.9)	72 (4.7)	149 (4.9)	70 (4.6)
Moderate	14 (0.5)	3 (0.2)	15 (0.5)	6 (0.4)
Severe	0	0	2 (0.1)	0
New or worsened muscle pain[c]				
Any	289 (9.3)	126 (8.2)	368 (12.0)	104 (6.8)
Mild	206 (6.7)	96 (6.3)	245 (8.0)	68 (4.5)
Moderate	82 (2.6)	30 (2.0)	122 (4.0)	36 (2.4)
Severe	1 (0.0)	0	1 (0.0)	0
New or worsened joint pain[c]				
Any	106 (3.4)	70 (4.6)	159 (5.2)	57 (3.7)
Mild	71 (2.3)	56 (3.7)	103 (3.4)	42 (2.8)
Moderate	35 (1.1)	14 (0.9)	56 (1.8)	15 (1.0)

	BNT162b2 Dose 1 N[a]=3096 n[b] (%)	Placebo Dose 1 N[a]=1531 to 1532 n[b] (%)	BNT162b2 Dose 2 N[a]=3064 n[b] (%)	Placebo Dose 2 N[a]=1521 to 1522 n[b] (%)
Severe	0	0	0	0
Use of antipyretic or pain medication[f]	436 (14.1)	135 (8.8)	601 (19.6)	111 (7.3)

Source: Adapted from Table 14.42 in the 6-Month Post-Dose 2 interim CSR for Study C4591007.
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 reaction.
c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
e. 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.
f. Severity was not collected for use of antipyretic or pain medication.

An overview of unsolicited adverse events from Dose 1 to one month after Dose 2 during the blinded placebo-controlled follow-up period is presented for the safety population in Table 9. Among participants who received at least 1 dose of study vaccine, unsolicited adverse events were reported by 333 (10.7%) participants in the BNT162b2 group and 150 (9.8%) participants in the placebo group. Lymphadenopathy were reported in 23 (0.7%) participants in the BNT162b2 group and 4 (0.2%) participants in the placebo group. Serious adverse events, from administration of Dose 1 to the participant unblinding date, were reported in 8 (0.3%) COMIRNATY recipients and in 2 (0.1%) placebo recipients. No serious adverse events were considered related to vaccination by the investigator.

Table 9. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Safety Population

	BNT162b2 (10 µg) (N=3109) n (%)	Placebo (N=1538) n (%)
Any adverse event	333 (10.7)	150 (9.8)
Related	109 (3.5)	32 (2.1)
Severe	5 (0.2)	1 (0.1)
Any serious adverse event	3 (0.1)	1 (0.1)
Related	0	0
Severe	3 (0.1)	1 (0.1)

Source: Adapted from Table 18 in the 6-Month Post-Dose 2 interim CSR for Study C4591007.

The safety population for the analysis of three doses of BNT162b2 (10 µg) included 2408 participants. Pain at the injection site was the most frequently reported local reaction, and the frequency was similar after each dose (Dose 1: 72.8%, Dose 2: 70.8%, Dose 3: 69.2%). Frequencies of any systemic event within 7 days after 3 doses of BNT162b2 (10 µg) were similar (Dose 1: 48.5%, Dose 2: 51.6%, Dose 3: 52.1%). Fatigue was the most frequently reported systemic event within 7 days after any dose. The frequencies of solicited adverse reactions reported in participants receiving a booster dose of BNT162b2

(10 μg) were generally consistent with those reported in pediatric participants receiving the first two doses of BNT162b2 (10 μg).

The percentage of participants reporting any AE from Dose 3 to one month after Dose 3 was 8.0% in the participants who received three doses of BNT162b2. Lymphadenopathy occurred in 46 (1.9%) participants who received a booster dose of BNT162b2 and in 23 (0.7%) participants who received BNT162b2 as a primary series. Serious adverse events from booster dose (Dose 3) through 6 months after Dose 3 were reported by 10 (0.4%) BNT162b2 recipients. No serious adverse events were considered related to vaccination by the investigator. There were no cases of myocarditis/pericarditis or deaths reported in the study as of the data cutoff date (February 28, 2023).

6.2 Trial #2: C4591048 (Substudy E)

A Master Phase 1/2/3 Protocol to Investigate the Safety, Tolerability, and Immunogenicity of Variant-Adapted BNT162b2 RNA-Based Vaccine Candidate(s) in Healthy Children

The clinical study reports (CSR) for Study C4591048 Substudy D and Substudy E were submitted to the sBLA. This memo focuses on the review of C4591048 Substudy E (SSE), which was a Phase 2/3 open-label study to evaluate the safety, tolerability, and immunogenicity of a single 10-μg dose of BNT162b2 (Omi XBB.1.5) in participants 5 to <12 years of age who were COVID-19 vaccine-naïve. The safety population included a total of 310 participants. C4591048 Substudy D (SSD) was a Phase 3 open-label study composed of 3 groups of participants to evaluate the safety, tolerability, and immunogenicity of a third or fourth dose of bivalent BNT162b2 (Original/Omi BA.4/ BA.5) at 10 μg, after receiving 2 or 3 prior doses of original monovalent BNT162b2. The safety population for C4591048 SSD consisted of a total of 134 participants.

6.2.1 Objectives

Primary Safety Objective: To describe the safety and tolerability profiles of prophylactic BNT162b2 (Omi XBB.1.5) given as a single dose in COVID-19 vaccine-naïve participants 5 to <12 years of age.

Primary Immunogenicity Objective: To immunobridge the Omicron XBB.1.5 immune response elicited by a single dose of BNT162b2 (Omi XBB.1.5) between COVID-19 vaccine-naïve participants 5 to <12 years of age who received a single 10-μg dose of BNT162b2 (Omi XBB.1.5), and vaccine-experienced participants ≥12 years of age who received a single dose of 30-μg BNT162b2 (Omi XBB.1.5) in C4591054 Substudy A (SSA).

Secondary Immunogenicity Objective: To describe the immune response to BNT162b2 (Omi XBB.1.5) as a single dose in COVID-19 vaccine-naïve participants 5 to <12 years of age.

6.2.2 Design Overview

C4591048 Substudy E was a Phase 2/3 open-label study to evaluate the safety, tolerability, and immunogenicity of a single age-appropriate dose of BNT162b2 (Omi XBB.1.5) in participants 5 to <12 years of age who were COVID-19 vaccine-naïve. Approximately 300 participants 5 to <12 years of age were enrolled.

6.2.3 Population

The study population comprised COVID-19 vaccine-naïve participants ≥5 years to <12 years of age at the time of enrollment.

6.2.4 Study Treatments or Agents Mandated by the Protocol

All subjects received a single vaccination intramuscularly into the deltoid muscle with monovalent BNT162b2 (Omicron XBB.1.5)

6.2.6 Sites and Centers

Thirty sites in the U.S., South Africa, and Brazil.

6.2.7 Surveillance/Monitoring

Please refer to clinical reviewer's memo.

6.2.8 Endpoints and Criteria for Study Success

Primary Safety Endpoints:

- Local reactions for up to 7 days following study vaccination
- Systemic events for up to 7 days following study vaccination
- AEs from study vaccination to 1 month after study vaccination
- SAEs from study vaccination to 6 months after study vaccination

Primary immunogenicity Endpoint:

- Geometric mean of SARS-CoV-2 Omicron XBB.1.5-neutralizing titers at 1 month after study vaccination
- Percentage of participants with seroresponse to Omicron XBB.1.5 at 1 month after study vaccination. Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a post vaccination assay result ≥4 × LLOQ is considered a seroresponse.

Success Criteria: For GMR, the lower limit of the 2-sided 95% CI is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8; for seroresponse rate difference, the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

Secondary Immunogenicity Endpoints:

- GMTs (geometric mean titers) at baseline and 1 month after the study vaccination
- GMFR (geometric mean fold rise) from baseline to 1 month after the study vaccination

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis populations

The safety population contained all subjects who entered the study and received one vaccination. Participants were summarized by vaccine group according to the study interventions they actually received.

The evaluable immunogenicity population included all eligible participants who received the study intervention to which they were assigned, had at least one valid and determinate immunogenicity result from the blood sample collected within an appropriate window (i.e., within 28 to 42 days after vaccination), and had no other important protocol deviations as determined by the clinician.

Primary immunogenicity analysis

GMR of SARS-CoV-2 Omicron XBB.1.5-neutralizing titers at 1 month after study vaccination for participants ≥5 to <12 years of age who received a single dose of BNT162b2 (Omi XBB.1.5) 10 μg to those at 1 month after study vaccination for Study C4591054 SSA participants ≥12 years of age who received a single dose of BNT162b2 (Omi XBB.1.5) 30 μg, and the associated 2-sided 95% CIs, were calculated by exponentiating the difference in least square (LS) means and the corresponding CIs based on the analysis of logarithmically transformed assay results using an ANCOVA model that included the baseline neutralizing titer, postbaseline infection status, age group (if applicable), and vaccine group as independent variables.

The difference in percentages of participants with seroresponse to Omicron XBB.1.5 at 1 month after study vaccination between participants ≥5 to <12 years of age who received a single dose of BNT162b2 (Omi XBB.1.5) 10 μg and Study C4591054 SSA participants ≥12 years of age who received a single dose of BNT162b2 (Omi XBB.1.5) 30 μg was provided with the associated 2-sided 95% CIs calculated using the Miettinen and Nurminen method, stratified by baseline neutralizing titer category (< median, ≥ median). The median of baseline neutralizing titers was calculated based on the pooled data in the two groups.

Sample size determination

For GMR, common assay standard deviations in log scale for Omicron XBB.1.5 neutralizing titers was assumed to be 1.5 based on data observed in Study C4591054. If the true GMR was 1.05 (GMT ratios of neutralizing titers at 1 month after study vaccination for participants in Study C4591048 SSE v.s. participants in Study C4591054 SSA), then 225 evaluable participants in each arm would provide 89.3% power to meet the noninferiority criteria. For seroresponse rate difference, if the seroresponse rate was 80% and 75% in Study C4591048 SSE and Study C4591054 SSA, respectively, then the power was 96.7% to meet the noninferiority criterion using a 10% margin.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The safety population included 310 participants. No participants were excluded from the

safety population for any reason. Most participants (92.6%) completed the study. Twenty-three participants (7.4%) withdrew from the study, with most withdrawals due to being lost to follow-up. The study populations for immunogenicity analyses included 310 participants 5 years to <12 years of age in Study C4591048 SSE and 303 participants ≥12 years of age in C4591054 SSA as the comparator group. The C4591048 SSE evaluable immunogenicity population included a total of 285 participants (91.9%) in the BNT162b2 (Omi XBB.1.5) 10-µg group. The C4591054 SSA evaluable immunogenicity population included a total of 302 participants (99.7%) in the BNT162b2 (Omi XBB.1.5) 30-µg group (Table 10).

Table 10. Analysis Populations in C4591048 SSE and C4591054 SSA

	C4591048 ≥5 to <12 Years	**C4591054 ≥12 Years**
	n (%)	n (%)
Assigned	310 (100.0)	303 (100.0)
Safety population	310 (100.0)	-
Evaluable immunogenicity population	285 (91.9)	302 (99.7)

Source: Adapted from Table 5 in the CSR for C4591048 Substudy E.

Reviewer's Comment:
A total of 25 subjects were excluded from the evaluable immunogenicity population in C4591048 Substudy E, of which 24 subjects did not have at least 1 valid and determinate immunogenicity result within 28-42 days after study vaccination, whereas only one subject was excluded in C4591054 Substudy A. In the IR response submitted to BLA 125742/656.12, the applicant clarified that participants from Study C4591054 SSA were matched by baseline SARS-CoV-2 infection status with Study C4591048 SSE participants. In addition, participants from Study C4591054 SSA were selected from those who had blood samples collected within 28 to 42 days after vaccination.

Regarding the demographic characteristics of C4591048 SSE and C4591054 SSA vaccine groups, participants 5 to <12 years of age in the C4591048 had higher proportions of Black or African American and Hispanic/Latino participants compared to the C4591054 comparator group of participants ≥12 years of age, due in part to enrollment of 5 to <12 year-old participants in both South Africa and Brazil in C4591048 SSE. Most participants in the C4591048 SSE were from the United States (n=194; 68.1%). All participants in the C4591054 SSA group were from the United States. The median ages were 7.0 years and 53.5 years in the C4591048 SSE and C4591054 SSA groups, respectively. The baseline SARS-CoV-2 status in the C4591048 SSE and comparator groups was generally similar and predominantly positive (Table 11). Demographic characteristics for participants in the safety population from C4591048 SSE were similar to those in the evaluable immunogenicity population from C4591048 SSE.

Table 11. Demographic Characteristics - C4591048 Substudy E and C4591054 Substudy A Participants – Evaluable Immunogenicity Population

	C4591048 SSE ⩾5 to <12 Years (N=285)	**C4591054 SSA ⩾12 Years (N=302)**
Age (years)		
Mean (std)	7.4 (1.97)	51.7 (18.77)
Median	7.0	53.5
Min, Max	5, 11	12, 82
Sex n (%)		
Female	153 (53.7)	176 (58.3)
Male	132 (46.3)	126 (41.7)
Race n (%)		
White	117 (41.1)	239 (79.1)
Black or African American	151 (53.0)	39 (12.9)
Asian	6 (2.1)	15 (5.0)
American Indian or Alaska Native	1 (0.4)	0
Native Hawaiian or other Pacific Islander	0	1 (0.3)
Multiracial	9 (3.2)	7 (2.3)
Not reported/Unknown	1 (0.4)	1 (0.3)
Ethnicity n (%)		
Hispanic/Latino	152 (53.3)	58 (19.2)
Non-Hispanic/non-Latino	133 (46.7)	242 (80.1)
Not reported	0	2 (0.7)
Baseline SARS-CoV-2 status n (%)		
Positive	282 (98.9)	300 (99.3)
Negative	3 (1.1)	2 (0.7)

Source: Adapted from Table 7 in the CSR for C4591048 Substudy E.

6.2.11 Immunogenicity Analyses

Primary Immunogenicity Endpoints

In the evaluable immunogenicity population, the primary model-based GMR of Omicron XBB.1.5-neutralizing titers for the BNT162b2 (Omi XBB.1.5) 10-µg group in C4591048 SSE to the BNT162b2 (Omi XBB.1.5) 30-µg group in C4591054 SSA was 1.81 (2-sided 95% CI: 1.51, 2.16). Immunobridging success criteria based on the model-based GMR were met since the lower limit of the 2-sided 95% CI for the GMR was greater than 0.67 and the point estimate of the GMR was ≥0.8 (Table 12).

Table 12. Geometric Mean Ratio Between C4591048 SSE and C4591054 SSA Participants at 1 Month After Study Vaccination - Evaluable Immunogenicity Population

	C4591048 SSE 5 Through 11 Years of Age		**C4591054 SSA ≥12 Years of Age**		**GMR[c] (95% CI[c])**
SARS-CoV-2 Neutralization Assay	n[a]	GMT[b] (95% CI[b])	n[a]	GMT[b] (95% CI[b])	
Omicron XBB.1.5 - NT50 (titer)	285	5930.5 (5283.8, 6656.4)	302	4006.4 (3438.3, 4668.4)	1.81 (1.51, 2.16)[d]

Source: Adapted from Table 9 in the CSR for C4591048 Substudy E.

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

b. 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.

c. GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on an ANCOVA model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.

d. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.

Reviewer's Comment:
The applicant included post-baseline infection status as a covariate in the ANCOVA model for the analysis of geometric mean ratio. According to ICH E9 guidelines, it is not advisable to adjust the main analyses for covariates measured after randomization because they may be affected by the treatments, therefore we recommended during IND that the applicant perform an analysis for the geometric mean ratio with those subjects who had post-baseline infection excluded. The applicant included this sensitivity analysis in the CSR, which showed a similar result to the primary model-based GMR presented in Table 12, i.e. the model-based GMR of Omicron XBB.1.5-neutralizing titers for the BNT162b2 (Omi XBB.1.5) 10-µg group to the BNT162b2 (Omi XBB.1.5) 30-µg group among participants without evidence of post-baseline infection was 1.80 (2-sided 95% CI: 1.50, 2.16).

In the evaluable immunogenicity population, 88.8% of participants in the C4591048 BNT162b2 (Omi XBB.1.5) 10-µg group and 77.0% of participants in the C4591054 BNT162b2 (Omi XBB.1.5) 30-µg group achieved seroresponse to Omicron XBB.1.5 (Table 13). The adjusted difference in percentages of participants with seroresponse between the BNT162b2 (Omi XBB.1.5) 10-µg group and BNT162b2 (Omi XBB.1.5) 30-µg group was 8.97% (95% CI: 3.91%, 14.02%). Immunobridging success criterion based on seroresponse rate was met since the lower limit of the 2-sided 95% CI for the adjusted difference in percentages of participants with seroresponse was >- 10%.

Table 13. Difference in Percentages of Participants With Seroresponse Between C4591048 SSE and C4591054 SSA Participants at 1 Month After the Study Vaccination – Evaluable Immunogenicity Population

	C4591048 SSE		C4591054 SSA		Difference	
SARS-CoV-2 Neutralization Assay	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	%[d]	95% CI[e]
Omicron XBB.1.5 - NT50 (titer)	285	253 (88.8) (84.5, 92.2)	300	231 (77.0) (71.8, 81.6)	8.97	(3.91, 14.02)[f]

Source: Adapted from Table 10 in the CSR for C4591048 Substudy E.

a. N = Number of participants with valid and determinate assay results for the specified assay both before vaccination and at the given sampling time point. This value is the denominator for the percentage calculations.

b. n = Number of participants with seroresponse for the given assay at the given sampling time point.

c. Exact 2-sided 95% CI based on the Clopper and Pearson method.

d. Adjusted difference in proportions based on the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median). The median of baseline neutralizing titers was calculated based on the pooled data in 2 comparator groups.

e. 2-sided 95% CI, based on the Miettinen and Nurminen method for the difference in proportions stratified by baseline neutralizing titer category (< median, ≥ median), expressed as a percentage.

f. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the adjusted difference in percentage of participants with seroresponse is greater than -10.0%.

Secondary Immunogenicity Endpoints

The GMT against Omicron XBB.1.5 was lower in the C4591048 BNT162b2 (Omi XBB.1.5) 10-µg group compared to the C4591054 BNT162b2 (Omi XBB.1.5) 30-µg group at pre-vaccination (GMT: 195.0 vs 355.1). At one month after vaccination, GMT was numerically higher in the BNT162b2 (Omi XBB.1.5) 10-µg group compared to that in the comparator group (Table 12).

GMFR against Omicron XBB.1.5 from before study vaccination to 1-month after vaccination was numerically higher in the C4591048 participants who received BNT162b2 (Omi XBB.1.5) 10 µg compared to that in the C4591054 participants who received BNT162b2 (Omi XBB.1.5) 30 µg (GMFR: 30.4 vs 11.3).

6.2.12 Safety Analyses

Table 14 and Table 15 present the frequences and severity of solicited local and systemic reactions, respectively, within 7 days following BNT162b2 (Omi XBB.1.5) 10 µg among participants 5 to <12 years of age in C4591048 SSE.

Pain at the injection site was the most frequently reported local reaction within 7 days after study vaccination (42.7%), followed by swelling (9.3%), and redness (6.0%). Most local reactions were mild or moderate in severity.

Table 14. Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination - Substudy E - Safety Population

	BNT162b2 (Omi XBB.1.5) Single Dose N[a]=302 n[b] (%)
Redness[c]	
Any (≥0.5 cm)	18 (6.0)
Mild	14 (4.6)
Moderate	4 (1.3)
Severe	0
Swelling[c]	
Any (≥0.5 cm)	28 (9.3)
Mild	18 (6.0)
Moderate	9 (3.0)
Severe	1 (0.3)
Pain at the injection site[d]	
Any	129 (42.7)
Mild	95 (31.5)
Moderate	34 (11.3)
Severe	0

Source: Adapted from Table 14.24 in the CSR for C4591048 Substudy E.
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 reaction.
c. Mild: ≥0.5 to <2.0 cm; Moderate: >2.0 to <7.0 cm; Severe: >7.0 cm.
d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Fatigue, headache, and muscle pain were the most frequently reported (range: 10%-15%) systemic events within 7 days after study vaccination, followed by diarrhea (~7%), chills (~6%), fever and joint pain (~5% for both), and vomiting (~4%). Most systemic events were mild or moderate in severity.

Table 15. Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination - Substudy E - Safety Population

	BNT162b2 (Omi XBB.1.5) Single Dose N[a]=302 n[b] (%)
Fever	
≥38.0°C	14 (4.7)
≥38.0°C to 38.4°C	6 (2.0)
>38.4°C to 38.9°C	5 (1.7)
>38.9°C to 40.0°C	1 (0.3)
>40.0°C	1 (0.3)
Unknown	1 (0.3)

	BNT162b2 (Omi XBB.1.5) Single Dose N[a]=302 n[b] (%)
Fatigue[c]	
Any	45 (14.9)
Mild	23 (7.6)
Moderate	20 (6.6)
Severe	2 (0.7)
Headache[c]	
Any	43 (14.2)
Mild	24 (7.9)
Moderate	18 (6.0)
Severe	1 (0.3)
Chills[c]	
Any	17 (5.6)
Mild	11 (3.6)
Moderate	6 (2.0)
Severe	0
Vomiting[d]	
Any	13 (4.3)
Mild	10 (3.3)
Moderate	3 (1.0)
Severe	0
Diarrhea[e]	
Any	22 (7.3)
Mild	18 (6.0)
Moderate	4 (1.3)
Severe	0
New or worsened muscle pain[c]	
Any	31 (10.3)
Mild	14 (4.6)
Moderate	17 (5.6)
Severe	0
New or worsened joint pain[c]	
Any	14 (4.6)
Mild	6 (2.0)
Moderate	8 (2.6)
Severe	0
Use of antipyretic or pain medication[f]	40 (13.2)

Source: Adapted from Table 14.27 in the CSR for C4591048 Substudy E.

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 reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. 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.
f. Severity was not collected for use of antipyretic or pain medication.

In the analysis of unsolicited adverse events, eleven participants (3.5%) reported AEs from the study vaccination through 1 month after the study vaccination. Three participants (1%) reported SAEs from study vaccination through 6 months after study vaccination. One SAE (Seizure) was considered to be related to study vaccination by the investigator. There were no cases of myocarditis/pericarditis or deaths reported from study vaccination through 6 months after study vaccination.

7. INTEGRATED OVERVIEW OF EFFICACY

Not applicable.

8. INTEGRATED OVERVIEW OF SAFETY

Not applicable.

9. ADDITIONAL STATISTICAL ISSUES

On May 27, 2025 and June 6, 2025, CBER requested concept sheets/protocols for the following three PMC studies, based on the New England Journal of Medicine article entitled "An Evidence-Based Approach to Covid-19 Vaccination", published on May 20, 2025 by the Commissioner and the CBER Center Director:

- Study 1: Prospectively designed study to evaluate safety and immunogenicity of COMIRNATY (2025-2026 Formula) in participants 65 years of age and older and 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. Please note that the study should be adequately powered for prespecified hypothesis testing of study immunogenicity endpoints for each age group in which COMIRNATY is approved for use.
- Study 2: A randomized, double-blind, saline placebo-controlled study to evaluate the efficacy and safety of COMIRNATY in individuals 50 through 64 years of age without underlying condition that puts them at high risk for severe outcomes from COVID-19.
- Study 3: Prospectively designed study to evaluate safety and immunogenicity of COMIRNATY (2025-2026 Formula) in participants: 5 years through 11 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

Statistical review of concept sheets for submitted PMC clinical studies

Concept Sheet For PMC Study 1

The applicant proposed a randomized, placebo-controlled, double-blind, crossover clinical study evaluating the safety, tolerability, and immunogenicity of a BNT162b2 (LP.8.1) adapted vaccine in participants 12 through 64 years of age that are considered at high risk for severe COVID-19 disease, and adults ≥65 years. This study will assess superiority of anti- LP.8.1 neutralizing titers following 1 dose of BNT162b2 (LP.8.1)

compared to 1 dose of placebo in each of these two age cohorts (12–64, and ≥65-year-old populations).

Population: Participants 12 through 64 years of age that are considered at high risk for severe COVID-19 disease, and adults ≥65 years. A total enrollment of approximately 880 participants is targeted. Participants 12 through 64 years of age will be considered at high risk of severe COVID-19 disease if they have any medical condition that puts them at higher risk of severe COVID-19 disease. Individuals with previous COVID-19 infection or vaccination will not be excluded from study enrollment unless the infection/vaccination has occurred within 3 months prior to study enrollment.

Primary Objectives:
Safety: To evaluate reactogenicity (evaluated for 7 days after vaccination in all study participants), and safety (all AEs for 1 month following vaccination; SAEs through 6 months following vaccination)
Immunogenicity: To demonstrate superiority of anti- LP.8.1 immune response after 1 dose of BNT162b2 (LP.8.1) as compared to after 1 dose of placebo given to participants 12–64 years of age at high risk of severe COVID-19 disease and ≥65 years of age

Design:
This study is designed as a randomized, double-blind study enrolling participants in two age cohorts. After signing informed consent, eligible participants 12 through 64 years and ≥65 years of age will be enrolled and randomized 3:1 to receive BNT162b2 (LP.8.1) on Day 1 and placebo at Day 28 OR to receive placebo at Day 1 and BNT162b2 (LP.8.1) on Day 28.

Statistical Considerations:
Statistical hypothesis testing for superiority for the primary objective will be conducted separately for each age group. No type I error adjustment will be applied across the age groups. Within each age group, superiority will be declared if the lower limit of the 2-sided 95% CI for the GMR of LP.8.1-neutralizing titers after receiving one dose of BNT162b2 (LP.8.1) to placebo is >1. A total number of at least 880 participants will be enrolled, with 440 participants enrolled in each age cohort (12-64 years of age at higher risk of severe COVID-19 disease, and ≥65 years of age).

Assuming a 10% non-evaluable rate in each age cohort, approximately 300 evaluable participants randomized to BNT162b2 (LP.8.1) and approximately 100 evaluable participants receiving placebo will contribute to each immunogenicity superiority evaluation. If the true GMR of LP.8.1-neutralizing titers after receiving one dose of BNT162b2 (LP.8.1) to placebo is 1.75, and the true common standard deviation is 1.5 for neutralizing titers at 1 month after vaccination in natural log scale, the study will provide 89.7% power to declare superiority under a 2-sided significance level of 0.05.

<u>Concept Sheet For PMC Study 2</u>
The applicant proposed a randomized, double-blind, placebo-controlled clinical study

evaluating the safety, tolerability, and efficacy of a BNT162b2 (LP.8.1) adapted vaccine in healthy participants 50-64 years of age. This study will assess the efficacy of BNT162b2 in the prevention of laboratory-confirmed COVID-19 disease following 1 dose of BNT162b2 (LP.8.1) compared to a placebo.

Population: Participants 50 through 64 years of age who do not have medical conditions that put them at a higher risk for severe COVID-19 disease. A total enrollment of at least 6000 participants is targeted.

Primary Objectives:
Safety: To evaluate reactogenicity (evaluated for 7 days after vaccination), safety (all AEs for 1 month following vaccination; SAEs throughout the entire study period) in all enrolled study participants
Efficacy: To evaluate the efficacy of BNT162b2 in the prevention of first occurrence of any laboratory confirmed, symptomatic COVID-19 case starting 7 days after vaccination

Design:
After signing informed consent, eligible participants 50 through 64 years of age will be enrolled and randomized 1:1 to BNT162b2 (LP.8.1) 30 μg or placebo. Reactogenicity data will be collected using an e-diary completed daily for 7 days. AEs will be collected through approximately 1 month after study vaccination. AESIs and SAEs will be collected through the entire study period (expected to be approximately 6 months after study vaccination or until the end of the COVID-19 case collection window, whichever is longer).

Statistical Considerations:
For the primary efficacy objective, the null hypothesis is that the VE of BNT162b2 to prevent first occurrence of any confirmed symptomatic COVID-19 case is ≤30% (i.e., H_0: VE ≤ 30%).

VE will be estimated as 100 × (1 – IRR), where IRR is the ratio of confirmed COVID-19 illness per 1000 person-years of follow up in the BNT162b2 group to the corresponding illness rate in the placebo group from 7 days after vaccination. The 95% CI of VE will be calculated using a conditional exact test based on the binomial distribution of the number of first-episode confirmed COVID-19 cases in the BNT162b2 group given the total number of first-episode cases in both groups, adjusted for surveillance time.

The primary analysis of efficacy will be performed in the evaluable efficacy population. If 10% of study participants are non-evaluable, at least 5400 participants will contribute to the primary efficacy analysis. Under the assumptions of true VE against COVID-19 being 50%, if the 6-month COVID-19 incidence rate is 8 to 12% in the placebo group, a total of 324 to 486 COVID-19 cases are expected to accrue during the study. The incidence rate will be reassessed against current epidemiology data prior to study start, and the sample size may be adjusted accordingly.

The primary analysis of efficacy will be conducted when at least 420 first-episode confirmed COVID-19 cases have been accrued. A total of 420 cases will provide approximately 90% power to reject the null hypothesis of true VE ≤30% at a 1-sided type I error rate of 2.5% to declare the efficacy of BNT162b2. An interim analysis may be performed when approximately 70% of target cases are accrued. The efficacy boundaries at interim analysis and final analysis will be calculated with an alpha-spending function to maintain the overall 1-sided 2.5% type I error rate.

Concept Sheet For PMC Study 3

The applicant proposed an open label clinical study to evaluate the safety, tolerability, and immunogenicity of a BNT162b2 (LP.8.1) adapted vaccine in children 5 through 11 years of age that are considered at high risk for severe COVID-19 disease. Participants will receive a single 10 μg dose of BNT162b2 (LP.8.1). This study will assess non-inferiority of anti- LP.8.1 neutralizing titers following 1 dose of BNT162b2 (LP.8.1) in children 5 through 11 years of age compared to neutralizing titers elicited after 1 dose of BNT162b2 (LP.8.1) given to adults 12 through 64 years of age in PMC Study 1 that are considered at high risk for severe COVID-19 disease.

Population: Participants 5 through 11 years of age that are considered at high risk for severe COVID-19 disease. A total enrollment of approximately 330 participants is targeted. Individuals with previous COVID-19 infection or vaccination will not be excluded from study enrollment unless the infection/vaccination has occurred within 3 months prior to study enrollment.

Primary Objectives:

Safety: To evaluate reactogenicity (evaluated for 7 days after vaccination in all study participants), safety (all AEs for 1 month following vaccination; SAEs through 6 months following vaccination)

Immunogenicity: To demonstrate non-inferiority of anti-LP.8.1 immune response after 1 dose of BNT162b2 (LP.8.1) in high-risk children ages 5 through 11 years in PMC Study 3 as compared to neutralizing titers elicited after 1 dose of BNT162b2 (LP.8.1) in high risk individuals 12 through 64 years of age in PMC Study 1.

Design:

The study is designed as an open label, single arm study.

Statistical Considerations:

Non-inferiority criterion is defined as the lower limit of the 2-sided 95% CI for the GMR of LP.8.1-neutralizing titer at 1 month after vaccination in children 5 through 11 years to titers in participants 12 through 64 years in PMC Study 1 is >0.67.

A total number of at least 330 participants will be enrolled in PMC Study 3 and compared with at least 330 participants in PMC Study 1. Assuming a 10% non-evaluable rate, approximately 300 evaluable participants in each group (enrolled in PMC Study 3 and PMC Study 1 respectively) will contribute to the immunogenicity non-inferiority evaluation. If the true GMR of LP.8.1-neutralizing titers after receiving 1 dose of

BNT162b2 (LP.8.1) is 1.0, and a common assay standard deviation of 1.5 for neutralizing titer results at 1 month after vaccination in natural log scale, the study will provide 91.1% statistical power to meet the non-inferiority criterion under a 2-sided significance level of 0.05.

Reviewer's Comments:
1. In an IR dated July 29, 2025, the review team recommended PMC study 3 to be incorporated into PMC study 1. Therefore, final PMC study 1 could potentially include 3 cohorts:
Cohort 1: ≥ 65 years of age (yoa);
Cohort 2: 12 yoa through 64 yoa at risk (Subchorts: 12 through 17 yoa; 18 through 64 yoa);
Cohort 3: 5 yoa through 11 yoa at risk,
with at least 330 vaccinees and 110 placebo subjects enrolled in each age cohort. The recommended study could be either a randomized, placebo-controlled, double-blind, crossover design, as proposed PMC study 1, or an open-label, single arm design. The recommended success criterion based on study design is as follows:
Placebo-controlled: lower bound of 95% CI for GMR of neutralizing titers after receiving vaccine to placebo >4 for each age group;
Single arm: lower bound of 95% CI for GMFR > 4 at Day 28 for each age group;
Comparison with adjacent age cohort: lower bound of 95% CI for GMR of neutralizing titers > 0.667 (with GMR point estimate > 0.85 or 95% CI that includes 1).
2. The sample size calculations in all PMC studies have been verified.
3. The PMC study protocols and statistical analysis plans will be submitted as an amendment to IND 19736. More specific comments about the protocols will be reviewed under the IND.

10. CONCLUSIONS

This statistical review focuses on clinical data supporting the expansion of the indication as well as the concept sheets for the PMC clinical studies. Specifically, the clinical data supporting the expansion of indication include 1) efficacy and safety data from vaccine-naïve participants 5 to <12 years of age in Study C4591007 following administration of a two dose series of the original monovalent BNT162b2 (10 μg), followed by a third dose of monovalent BNT162b2 (10 μg); and 2) immunogenicity and safety data in vaccine-naïve participants 5 to <12 years of age in C4591048 Substudy E following administration of a single dose of BNT162b2 (Omi XBB.1.5) at 10 μg.

C4591007
A total of approximately 4500 participants 5 to <12 years of age were enrolled in the Phase 2/3 portion of Study C4591007 and randomized in a 2:1 ratio to receive the original monovalent BNT162b2 (10 μg) or placebo as a 2-dose series.

In the evaluable efficacy (2-dose) population without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2 (n = ~4000), the observed vaccine efficacy (VE) among 5 to <12 years of age was 88.2% (2-sided 95% CI: 76.2%, 94.7%) for first COVID-19 cases confirmed from ≥7 days after Dose 2 to before Dose 3 through the blinded follow-up

period, meeting the predefined success criterion as the lower limit of the 95% CI for VE was >30%. A descriptive analysis of VE in participants 5 years through 11 years of age with at least one comorbidity of interest without evidence of prior SARS-CoV-2 infection was 92.3% (2-sided 95% CI: 66.0%, 99.2%).

In both BNT162b2 (10 µg) and placebo groups, pain at the injection site was the most frequently reported local reaction (72.9% and 31.5% after Dose 1, in the BNT162b2 and placebo groups, respectively; 71.2% and 28.5% after Dose 2, in the BNT162b2 and placebo groups, respectively). In the BNT162b2 group, most systemic events were reported at higher frequencies and severity after Dose 2 compared to after Dose 1, with the exceptions of vomiting and diarrhea, both of which were reported infrequently and at similar frequencies after each dose. After Dose 2, most systemic events were reported less frequently in the placebo group compared with the BNT162b2 group. Overall, the numbers of participants reporting any adverse events (AEs) from Dose 1 to 1 month after Dose 2 were similar in the BNT162b2 (10.7%) and placebo (9.8%) groups. Any related AEs and any serious adverse events (SAEs) were reported in the BNT162b2 and placebo groups by ≤3.5%, and 0.1%, respectively. There were no cases of myocarditis/pericarditis or deaths reported in the study as of the data cutoff date (February 28, 2023).

C4591048

Approximately 300 COVID-19 vaccine–naïve participants 5 to <12 years of age were enrolled in Substudy E and received a single 10-µg dose of BNT162b2 (Omi XBB.1.5). Omicron XBB.1.5-neutralizing titers at 1 month after study vaccination was compared to a group of vaccine-experienced participants ≥12 years of age who received a single 30-µg dose of BNT162b2 (Omi XBB.1.5) in C4591054 Substudy A.

In the evaluable immunogenicity population, model-based geometric mean ratio (GMR) of Omicron XBB.1.5-neutralizing titers for the BNT162b2 (Omi XBB.1.5) 10-µg group in C4591048 SSE (n=285) to vaccine-experienced participants ≥12 years of age who received a single 30-µg dose of BNT162b2 (Omi XBB.1.5) in C4591054 Substudy A (n=302) was 1.81 (2-sided 95% CI: 1.51, 2.16). The adjusted difference in percentages of participants with seroresponse between the BNT162b2 (Omi XBB.1.5) 10-µg group and BNT162b2 (Omi XBB.1.5) 30-µg group was 8.97% (95% CI: 3.91%, 14.02%). The immunobridging success criteria were met since the lower limit of the 2-sided 95% CI was greater than 0.67and the point estimate was ≥0.8 for GMR, and the lower limit of the 2-sided 95% CI for the adjusted difference in percentages of participants with seroresponse was >-10%.

Pain at the injection site was the most frequently reported local reaction within 7 days after study vaccination (43%). Fatigue, headache, and muscle pain were the most frequently reported (range: 10%-15%) systemic events within 7 days after study vaccination. Eleven participants (3.5%) reported AEs from the study vaccination through 1 month after the study vaccination. Three participants (1%) reported SAEs from study vaccination through 6 months after study vaccination, one of which (seizure) was considered to be related by the investigator. There were no cases of myocarditis/

pericarditis or deaths reported from study vaccination through 6 months after study vaccination.

Overall, Study C4591007 met the success criteria for the secondary efficacy endpoint; Study C4591048 SSE met the success criteria for the primary immunogenicity endpoints. I defer to the clinical reviewer on the safety assessment of this vaccine and the regulatory action for this sBLA.