Application Type	BLA Supplement
STN	125742/276
CBER Received Date	February 23, 2023
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Division / Office	DVRPA/OVRR
Committee Chair	Michael Smith
Clinical Reviewer(s)	Adam Spanier
Project Manager	Meghan Maguire Thon Julianne Clifford
Priority Review	No
Reviewer Name(s)	Ruoxuan Xiang
Review Completion Date / Stamped Date	
Concurrence	Lei Huang Concurring Reviewer, Vaccine Evaluation Branch (VEB), Division of Biostatistics (DB), Office of Biostatistics and Pharmacovigilance (OBPV)
	Tsai-Lien Lin Branch Chief, VEB/DB/OBPV
Applicant	BioNTech and Pfizer
Established Name	BNT162b2
(Proposed) Trade Name	COMIRNATY
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Each 0.3 mL dose of COMIRNATY (2023-2024 Formula) is formulated to contain 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5)
Dosage Form(s) and Route(s) of Administration	30 μg RNA dose 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 coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older

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1. Executive Summary

BioNTech and Pfizer, the applicant, submitted a supplemental Biologics License Application (sBLA), STN 125742/276, for the BNT162b2 vaccine for active immunization to prevent Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

The initial submission was to seek approval of the BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) vaccine at the 30 μg dose level as a 2-dose primary series and booster(s). The submission included immunogenicity data (i.e., neutralization titers against Omicron BA.4/BA.5 and reference strain) and safety data from participants in Cohort 2 (≥12 years of age) and Cohort 3 (≥18 years of age) of Study C4591044 following administration of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 or 60 μg as a booster after receiving 3 prior doses of BNT162b2. The intent of this sBLA was modified to seeking authorization of the single dose use regardless of previous vaccination status after April 18, 2023, when the Food and Drug Administration (FDA) amended the emergency use authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine, Bivalent to simplify the vaccination schedule to a single dose use for most individuals.

On June 2, 2023, CBER requested for a single dose study in COVID-19 vaccine naïve, baseline SARS-CoV-2 positive individuals 12 years of age and older during a teleconference between CBER and the applicant. On June 16, 2023, FDA recommended Pfizer/BioNTech to develop a monovalent (XBB.1.5 variant) COVID-19 vaccine for age-appropriate use in potentially eligible populations based on the Vaccines and Related Biological Products (VRBPAC) meeting held on June 15, 2023 regarding the SARS-CoV-2 strain composition for the 2023-2024 Formula for COVID-19 vaccines. On June 23, 2023, the applicant submitted to STN 125742/276.16 the updated package to support licensure of the 30-μg COMIRNATY 2023-2024 Formula for use in individuals ≥12 years of age irrespective of previous COVID-19 vaccination status. The applicant submitted to STN 125742/276.25 the data derived from Study BNT162-17 to support the use of a single dose of COMIRNATY in seropositive individuals not previously vaccinated with a COVID-19 vaccine which included immunogenicity results after a single 30μg dose of an modified bivalent BNT162b2 (B.1.1.7 + B.1.617.2, or Alpha/Delta strains) vaccine in COVID19 vaccine-naïve participants ≥18 to ≤85 years of age who had evidence of prior SARS-CoV-2 infection and immunogenicity results from a comparator subset of COVID19 vaccine-naïve participants with no evidence of SARS-CoV-2 infection who received 2 doses of the original BNT162b2 vaccine at 30 μg in Study C4591001.

As a post-approval commitment, the applicant proposed an additional substudy (Substudy B) of C4591054 in which previously SARS-CoV-2 exposed, vaccine-naïve individuals 12 years of age and older will be assessed for immunogenicity 1 month after receipt of 30 μg monovalent (XBB.1.5 variant) COVID-19 vaccine.

This review memo focuses on the statistical review of the immunogenicity and safety data from Study C4591044 (Cohorts 2 and 3) and the immunogenicity data from Study BNT162-17 (Part B Cohort 6).

Study C4591044

This is a Phase 2/3 ongoing, randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of new bivalent vaccines. Combining Cohort 2 and Cohort 3, there were approximately 300 participants in each age group (>55 years and 18-55 years of age) who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg.

The primary immunogenicity objective of Study C4591044 was to assess the superiority with respect to geometric mean titer (GMT) of neutralizing titer and noninferiority (NI) with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent 30 µg in the >55-year age group relative to the anti-Omicron immune response elicited by BNT162b2 (reference strain) 30 µg in the >55-year age group from C4591031 Substudy E, where seroresponse was defined as a ≥4-fold rise from baseline. Model-based geometric mean ratio (GMR) of neutralizing titers for participants >55 years of age in the BNT162b2 Bivalent 30-µg group to C4591031 Substudy E participants >55 years of age in the BNT162b2 (reference strain) 30-µg group was 2.91 (95% CI: 2.45, 3.44), meeting the success criterion that the lower confidence limit is >1. The adjusted difference in seroresponse rates between the BNT162b2 Bivalent 30-µg group and the BNT162b2 30-µg group was 26.77 % (95% CI: 19.59%, 33.95%), meeting the noninferiority criterion, as the lower bound (LB) of the 95% CI for the difference in seroresponse rates was > -5%.

An additional primary immunogenicity objective was to assess the noninferiority with respect to level of neutralizing titer and seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent 30 µg in the 18 through 55-year age group relative to the immune response induced by BNT162b2 Bivalent 30 µg in the >55-year age group within Study C4591044. Model-based GMR of neutralizing titers for participants 18 through 55 years of age to >55 years of age was 0.98 (95% CI: 0.83, 1.16), meeting the noninferiority criterion, as the LB of the 95% CI for GMR was >0.67. Noninferiority in terms of the difference in seroresponse rates was also demonstrated for participants 18 to 55 years of age to those >55 years of age as the adjusted LB of the 95% CI for the difference in seroresponse rates was -9.68%, which was greater than the pre-specified NI margin of -10%.

The primary safety objective for Cohorts 2 and 3 was to describe the safety and tolerability profile of BNT162b2 Bivalent 30 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55 and >55 years of age. Available safety data for participants 12 through 17 (n=107), 18 through 55 (n=313) and >55 years of age (n=306) included local reactions and systemic events recorded in the e-diary for 7 days after vaccination and adverse events (AEs) reported through 1 month after vaccination.

Pain at the injection site was the most frequently reported local reaction within 7 days after booster dose (by 70.1%, 76.1% and 57.1% of the participants 12 through 17, 18 through 55 and >55 years of age, respectively). Swelling and redness at the injection site were reported less frequently. Fatigue was the most frequently reported systemic event within 7 days after booster dose (by 67.3%, 61.2% and 38.5% of the participants 12 through 17, 18 through 55 and >55 years of age, respectively), followed by headache, muscle pain, and chills. Most local reactions and systemic events were mild or moderate in severity.

Eight (7.5%) participants 12 through 17 years of age, 19 (6.1%) participants 18 through 55 years of age and 21 (6.9%) participants >55 years of age reported any AE through 1 month after vaccination. One (0.3%) Serious AE (SAE) was reported by a participant 18 through 55 years of age and 2 (0.7%) SAEs were reported by participants >55 years of age. No life-threatening AEs, withdrawals due to AEs, or deaths were reported.

Study BNT162-17

BNT162-17 was a Phase 2, open-label study to investigate the safety and immunogenicity of BNT162b2-based vaccines against variant strains. This study consisted of 3 parts: Part A, Part B, and Part C. Part B included participants ≥18 to ≤85 years old in 3 cohorts (Cohort 1, Cohort 4, and Cohort 6) with approximately 375 participants each. An ad-hoc analysis of data from Part B Cohort 6 were used to evaluate the immunogenicity of a first dose of variant (Alpha/Delta)-modified BNT162b2 bivalent (B.1.1.7 + B1.617.2) vaccine in COVID-19 vaccine-naïve participants who had evidence of prior SARS-CoV-2 infection (seropositive).

The primary immunogenicity objective was to assess the noninferiority of the reference strain immune response at 3 weeks after 1 dose (hereafter referred to as “3W PD1”) of BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve seropositive participants in Study BNT162-17 Part B Cohort 6 to that at 1 month after 2 doses (hereafter referred to as “1M PD2”) of BNT162b2 (reference strain) in seronegative participants in Study C4591001 in terms of geometric mean titer (GMT) and seroresponse rate.

Model-based GMR of reference strain neutralizing titer in the BNT162-17 bivalent BNT162b2 group at 3W PD1 to that in the C4591001 original BNT162b2 group at 1M PD2 was 13.12 (95% CI: 11.14, 15.45), meeting the noninferiority criterion, as the LB of the 95% CI for GMR was >0.67. The adjusted difference in seroresponse rates between the BNT162-17 bivalent BNT162b2 group and the C4591001 original BNT162b2 group was -4.55% (95% CI: -10.04%, 0.83%), failing to meet the noninferiority criterion, as the LB of the 95% CI was marginally lower than the noninferiority threshold of -10%, in part because the BNT162-17 bivalent BNT162b2 group had much higher pre-vaccination titers than the C4591001 original BNT162b2 group due to prior SARS-CoV-2 infection, which requires much higher post-vaccination titers to achieve ≥4-fold rise.

Conclusion

The pre-specified success criteria for the primary immunogenicity endpoints were met in

both Study C4591044 and Study BNT162-17 except for the seroresponse rate endpoint in Study BNT162-17. No significant safety concerns were identified in the study populations. I defer to the clinical reviewer on the acceptability of the totality of the immunogenicity and safety data regarding single dose use of the BNT162b2 (2023-2024 Formula) vaccine in individuals 12 years of age and older regardless of previous vaccination status.

2. CLINICAL AND REGULATORY BACKGROUND

On April 18, 2023, the FDA amended the EUA of Pfizer-BioNTech COVID-19 Vaccine, Bivalent to simplify the vaccination schedule for most individuals. This action included authorizing the current bivalent vaccine (Original and Omicron BA.4/BA.5 strains) to be used in an appropriate schedule based on age, previous vaccination status and risk of COVID-19-associated severe disease, hospitalization, and death.

On June 16, 2023, the FDA recommended Pfizer/BioNTech to develop a monovalent (XBB.1.5 variant) COVID-19 vaccine for age-appropriate use in potentially eligible populations based on the Vaccines and Related Biological Products (VRBPAC) meeting held on June 15, 2023 regarding the SARS-CoV-2 strain composition for the 2023-2024 Formula for COVID-19 vaccines. On June 23, 2023, the applicant submitted to STN 125742/276.16 the updated package to support licensure of the 30-µg COMIRNATY 2023-2024 Formula for use in individuals ≥12 years of age irrespective of previous COVID-19 vaccination status. An ad-hoc analysis of data derived from Study BNT162-17 to support the use of a single dose of COMIRNATY in seropositive individuals not previously vaccinated with a COVID-19 vaccine was submitted to STN 125742/276.25. The raw datasets for Study BNT162-17 were submitted to STN 125742/276.30.

As a post-approval commitment, the applicant proposed an additional substudy (Substudy B) of C4591054 in which previously SARS-CoV-2 exposed, vaccine-naïve individuals 12 years of age and older will be assessed for immunogenicity 1 month after receipt of 30 µg monovalent (XBB.1.5 variant) COVID-19 vaccine. The study protocol was submitted to and reviewed under IND 19736.1151.

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 in the main studies 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

The statistical review of this sBLA comprises two parts: clinical (immunogenicity and safety) and clinical assay data. This review focus on the clinical data; the review of clinical assay is documented in a separate memo.

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

The following submissions were reviewed:

- STN 125742/276.0 Module 2, Module 5
- STN 125742/276.5 Module 1.11.3
- STN 125742/276.16 Module 2
- STN 125742/276.25 Module 5.3.5.1
- STN 125742/276.30 Module 5.3.5.1
- STN 125742/276.59 Module 1.11.3, Module 5.3.5.1

5.3 Table of Studies/Clinical Trials

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

Table 1. Overview of Clinical Studies

Study Number	Description	BNT162b2 N	Placebo N
C4591044	Phase 2/3 randomized, active-controlled study to evaluate safety and immunogenicity of Bivalent BNT162b RNA-based vaccine candidates as a booster dose in COVID-19 vaccine–experienced individuals	Cohort 2: 530 Combined Cohort 2 (Group 2 and Group 4) and Cohort 3: 620	0
BNT162-17	Phase 2 study to evaluate safety and immunogenicity of SARS-CoV-2 monovalent and multivalent RNA-based vaccines - [only immunogenicity data from this study are reviewed]	262	0

Source: Adapted from Tables 5 and 6 in C4591044-interim-c2-c3-mth1-report-body.pdf submitted to STN 125742/276.0, and Table 3 in BNT162-17-single-dose-immuno-data.pdf submitted to STN 125742/276.25.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: C4591044

An Interventional, Randomized, Active-Controlled, Phase 2/3 Study To Investigate The Safety, Tolerability, and Immunogenicity of Bivalent BNT162b RNA-Based Vaccine Candidates as a Booster Dose in COVID-19 Vaccine-Experienced Healthy Individuals ≥12 years of age

6.1.1 Objectives

Primary Safety:
Cohort 2: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age, and BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.

Cohorts 2 and 3: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.

Primary Immunogenicity:

1. Cohort 2/Group 4 and Cohort 3/Group 2 combined: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg given as a second booster dose to BNT162b2-experienced participants >55 years of age.
2. Cohort 2/Group 2 and Cohort 3/Group 1 combined and Cohort 2/Group 4 and Cohort 3/Group 2 combined: To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age.
3. Cohort 2: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age.

Secondary Immunogenicity:
Cohort 2/Group 4 and Cohort 3/Group 2 Combined: To demonstrate the noninferiority of the anti-reference-strain immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg given as a second booster dose in BNT162b2-experienced participants >55 years of age.

6.1.2 Design Overview

This is an ongoing Phase 2/3 randomized, active-controlled clinical study to evaluate the safety, tolerability and immunogenicity of bivalent BNT162b2 as booster doses in experienced study participants. Cohort 1 evaluated the BNT162b5 Bivalent (WT/OMI BA.2) or BNT162b2 Bivalent (WT/OMI BA.1) vaccine candidate and was not pertinent to this sBLA. Cohort 2 and Cohort 3 evaluated BNT162b2 Bivalent (WT/OMI

BA.4/BA.5) 30 µg or 60 µg (Table 2). Cohort 3 and Group 1 of Cohort 2 were conducted in an open-label fashion, while Groups 2-5 of Cohort 2 were randomized 1:1 to receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at either 30 µg or 60 µg and observer blind.

6.1.3 Population

Eligible study participants were healthy male or female individuals ≥12 years of age who received 3 prior doses of BNT162b2 (30 µg), with the last dose administered 150 to 365 days before Visit 1 (Day 1).

6.1.4 Study Treatments or Agents Mandated by the Protocol

A single dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 or 60 µg was administered. Table 2 summarizes the treatment groups for Cohorts 2 and 3.

Table 2. Cohort 2 and Cohort 3 Design in Study C4591044

Cohort/ Group	Participant Age Group (years)	Prior Doses of BNT162b2	Time since last dose (days)	Study Dose	Number of Participants Planned
Cohort 2	-	-	-	-	-
Group 1	12-17	3	150-365	30 µg	100
Group 2	18-55	3	150-365	30 µg	100
Group 3	18-55	3	150-365	60 µg	100
Group 4	>55	3	150-365	30 µg	100
Group 5	>55	3	150-365	60 µg	100
Cohort 3	-	-	-	-	-
Group 1	18-55	3	150-365	30 µg	200
Group 2	>55	3	150-365	30 µg	200

Source: Adapted from Tables 2 and 3 in C4591044-interim-c2-c3-mth1-report-body.pdf submitted to STN 125742/276.0.

6.1.5 Directions for Use

Please refer to Dr. Adam Spanier's clinical review memo.

6.1.6 Sites and Centers

Thirty clinical study sites in the United States.

6.1.7 Surveillance/Monitoring

Please refer to Dr. Adam Spanier's clinical review memo.

6.1.8 Endpoints and Criteria for Study Success

Primary Safety Endpoints:

- Local reactions within 7 days after study vaccination
- Systemic events within 7 days after study vaccination
- AEs from the study vaccination through 1 month after the study vaccination
- SAEs from the study vaccination through 6 months after the study vaccination

Primary Immunogenicity Endpoint:
Neutralizing titer (NT) against SARS-CoV-2 Omicron (BA.4/BA.5)

Secondary Immunogenicity Endpoint:
Neutralizing titer (NT) against SARS-CoV-2 reference strain

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis Sets
The randomized population included all participants who were assigned with a randomization number in the interactive response technology (IRT) system. The safety population included all participants who received at least 1 dose of the study intervention.

The evaluable immunogenicity population included all eligible randomized participants who received the study intervention to which they were randomized/assigned, had at least 1 valid and determinate immunogenicity result from the blood sample collected within 28-42 days after the study vaccination, and had no other important protocol deviations as determined by the clinician. For all the immunogenicity endpoints, the analyses were based on the evaluable immunogenicity population.

Success criteria and statistical methods for the primary immunogenicity analysis
For participants >55 ages (Cohort 2/Group 4 and Cohort 3/Group 2):
The primary immunogenicity objective was to assess the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group relative to the anti-Omicron immune response elicited by BNT162b2 30 µg in the >55-year age group from C4591031 Substudy E. Seroresponse was defined as a ≥4-fold rise from baseline. If the baseline measurement was below the lower limit of quantitation (LLOQ), the postvaccination measure of ≥4 × LLOQ was considered a seroresponse. Superiority based on GMR would be declared if the lower limit of the 2-sided 95% CI for the GMR was greater than 1; noninferiority based on seroresponse would be declared if the LB of the 2-sided 95% CI for the difference in seroresponse rates was >-5%.

For the 18- to 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1 combined):
The primary immunogenicity objective was to assess the noninferiority with respect to level of neutralizing titer and seroresponse rate of the anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18 through 55-year age group (Cohort 2/Group 2 + Cohort 3/Group 1) relative to the anti-Omicron immune response elicited by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the >55-year age group (Cohort 2/Group 4 +Cohort 3/Group 2). Noninferiority based on GMR was declared if the lower limit of the 95% CI for the GMR was greater than 0.67; noninferiority based on seroresponse was declared if the lower limit of the 95% CI for the difference in seroresponse rates was >-10%.

Model-based GMRs and the associated 95% CIs along with the model-based least square (LS) GMTs and associated 95% CIs were calculated using the linear regression model

that included terms for baseline neutralizing titer and comparison group. The difference in percentages of participants with seroresponse and the associated 2-sided 95% CIs were calculated using the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median). The median of baseline neutralizing titers was calculated based on the pooled data in 2 comparator groups.

Success criteria and statistical methods for the Secondary immunogenicity analysis
The secondary immunogenicity objective was to assess the noninferiority of the anti–reference-strain immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 μg in the >55-year age group relative to the anti-reference strain immune response elicited by BNT162b2 30 μg in the >55-year age group from C4591031 Substudy E. Noninferiority based on the GMR would declared if 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.

The primary and secondary objectives were evaluated sequentially using 1-sided alpha of 0.025. The primary objective for the >55-age group was evaluated first, followed by the secondary objective of the GMR of the anti-reference strain immune response for the >55-age group, and then the primary objective for the 18 through 55 age group. The later objective was evaluated only if the previous objectives were met. The primary objectives involved 2 hypotheses: GMR and seroresponse rate difference. Both hypotheses within the objective must be established before evaluating the next objective in the sequence. Therefore, the overall type I error was controlled.

The safety analyses were based on the safety population. Percentages and associated Clopper-Pearson 95% CIs of AEs were summarized for each group.

Sample Size Calculations
Approximately 500 participants were planned for enrollment into Cohort 2 and 400 participants were planned for enrollment into Cohort 3. Using a historical comparator consisting of 300 participants from C4591031 Substudy E and assuming a 20% non-evaluable rate, 480 evaluable participants were planned for the immunogenicity evaluations.

For the >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined vs. BNT162b2 30-μg group from C4591031 Substudy E):
For comparisons based on GMR, the standard deviation of neutralizing antibody titers at 1 month after the third or fourth dose in log scale was assumed to be 1.45 based on data observed in the C4591031 Substudy E. If the true GMR of Omicron-neutralizing titer in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-μg group to the BNT162b2 30-μg group was 1.5, then 480 evaluable participants would provide 86.4% power to declare superiority. For comparisons based on seroresponse rate, if the seroresponse rate was 65% in the BNT162b2 Bivalent 30-μg group and 52% in the BNT162b2 30-μg group, the study had 98.0% power to demonstrate noninferiority using a 5% margin.

For the 18- through 55-age group (Cohort 2/Group 2 + Cohort 3/Group 1 combined)

vs. >55-age group (Cohort 2/Group 4 + Cohort 3/Group 2 combined):
For comparisons based on GMR, if the true GMR of Omicron-neutralizing titer after BNT162b2 Bivalent 30 µg in the 18- through 55-age group to the >55-age group was 1, then 480 evaluable participants (240 in the 18- through 55-age group and 240 in the >55-age group) would provide 86.4% power to declare noninferiority. For comparisons based on seroresponse rate, if the seroresponse rate after BNT162b2 Bivalent 30 µg was 65% in the 18- through 55-age group and 65% in the >55-age group, the study had 63.4% power to demonstrate noninferiority using a 10% margin.

6.1.10 Study Population and Disposition

The safety population included 619 participants who received BNT162b2 Bivalent 30 µg: 313 participants who were 18 through 55 years of age and 306 participants who were >55 years of age (Table 3). The evaluable immunogenicity population for participants included a total of 297 and 286 participants 18 through 55 and >55 years of age in the BNT162b2 Bivalent 30-µg groups, respectively, and 289 participants >55 years in the BNT162b2 30-µg group from Study C4591031. There were 17 exclusions for participants 18 through 55 and 20 exclusions for participants >55 years of age in the BNT162b2 Bivalent 30-µg groups from the evaluable immunogenicity population, with the majority being due to not having at least 1 valid and determinate immunogenicity result within 28-42 days after the study vaccination.

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

-	**C4591044 BNT162b2 Bivalent 30 µg 18-55 Years**	**C4591044 BNT162b2 Bivalent 30 µg >55 Years**	**C4591031 BNT162b2 30 µg >55 Years**
-	n	n	n (%)
Randomized population	314 (100.0)	306 (100.0)	289 (100.0)
Vaccinated (Safety population)	313 (99.7)	306 (100.0)	-
Evaluable immunogenicity population	297 (94.6)	286 (93.5)	289 (100.0)

Source: Adapted from Tables 8 and 13 in C4591044-interim-c2-c3-mth1-report-body.pdf submitted to STN 125742/276.0.

Demographic characteristics of participants 18-55 years of age and >55-years in the BNT162b2 Bivalent 30-µg groups and participants >55 years in the BNT162b2 30-µg group are shown in Table 4 (evaluable immunogenicity population). Female participants made up 65.0% and 54.9% of participants 18 through 55 and >55 years of age, respectively, in the BNT162b2 Bivalent 30-µg groups, and 53.6% of participants >55 years of age in the BNT162b2 30-µg group. Most participants 18-55 years of age and >55-years in the BNT162b2 Bivalent 30-µg groups were White (80.5% and 78.3%, respectively), and 87.9% of participants >55 years in the BNT162b2 30-µg group were

White. The demographics of the safety population for BNT162b2 Bivalent 30-µg groups in Study C4591044 were similar to that of the evaluable immunogenicity population.

Table 4. Baseline Demographics – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Evaluable Immunogenicity Population

Demographics	C4591044 BNT162b2 Bivalent 30 µg 18-55 Years (N=297) n (%)	C4591044 BNT162b2 Bivalent 30 µg >55 Years (N=286) n (%)	C4591031 BNT162b2 30 µg >55 Years (N= 289) n (%)
Sex	-	-	
Male	104 (35.0)	129 (45.1)	134 (46.4)
Female	193 (65.0)	157 (54.9)	155 (53.6)
Race	-	-	
White	239 (80.5)	224 (78.3)	254 (87.9)
Black or African American	25 (8.4)	47 (16.4)	18 (6.2)
American Indian or Alaska Native	0	3 (1.0)	0
Asian	30 (10.1)	8 (2.8)	12 (4.2)
Native Hawaiian or Pacific Islander	0	1 (0.3)	2 (0.7)
Multiracial	3 (1.0)	3 (1.0)	3 (1.0)
Ethnicity	-	-	
Hispanic/Latino	39 (13.1)	37 (12.9)	54 (18.7)
Not Hispanic/Latino	256 (86.2)	247 (86.4)	235 (81.3)
Not reported	2 (0.7)	2 (0.7)	0
Mean Age (Min, Max)	39.2 (18, 55)	65.6 (56, 87)	66.3 (56, 87)

Source: Adapted from Table 19 in C4591044-interim-c2-c3-mth1-report-body.pdf submitted to STN 125742/276.0.

6.1.11 Efficacy and Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoints

Omicron BA.4/BA.5 GMRs and Difference in Seroresponse rates in participants >55 years of age

In the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination, model-based GMR of Omicron BA.4/BA.5 neutralizing titer for participants >55 years of age in the BNT162b2 Bivalent 30-µg group to C4591031 Substudy E participants >55 years of age in the BNT162b2 30-µg group was 2.91 (95% CI: 2.45, 3.44) (Table 5). The superiority criterion of BNT162b2 Bivalent 30 µg to BNT162b2 30 µg in the >55-year age group was met, as the lower bound of the 95% CI for GMR was >1. A similar analysis was also performed for participants without prior evidence of infection and resulted in a GMR of 3.37 (95% CI: 2.66, 4.29).

Table 5. Model-Based Geometric Mean Ratios – Evaluable Immunogenicity Population 1 Month Postvaccination – Study C4591031 and Combined Cohorts 2 and 3 in Study C4591044

SARS-CoV-2 neutralization assay	C4591044 BNT162b2 Bivalent (18-55 YOA) n[a] [GMT (95% CI)]	C4591044 BNT162b2 Bivalent (>55 YOA) n[a] [GMT (95% CI)]	C4591031 BNT162b2 Substudy E (>55 YOA) n[a] [GMT (95% CI)]	C4591044 (18-55 YOA) / C4591031 (>55 YOA) GMR (95% CI)	C4591044 (18-55 YOA) / C4591044 (>55 YOA) GMR (95% CI)
Omicron BA.4/BA.5 - NT50 (titer)	-	282 [3373.4 (3000.3, 3793.0)]	273 [1160.7 (1030.3, 1307.7)]	2.91 (2.45, 3.44)	-
Omicron BA.4/BA.5 - NT50 (titer)	294 [4254.2 (3779.6, 4788.4)]	282 [4344.4 (3850.2, 4902.1)]	-	-	0.98 (0.83, 1.16)
Reference strain - NT50 (titer)	-	284 [15361.6 (14082.9, 16756.5)]	287 [11117.2 (10196.4, 12121.1)]	1.38 (1.22, 1.56)	-

a. n = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.
Source: Adapted from Table 37 in C4591044-interim-c2-c3-mth1-report-body.pdf submitted to STN 125742/276.0.

The noninferiority of 30µg BNT162b2 Bivalent (WT/OMI BA.4/BA.5) with respect to the anti-Omicron BA.4/BA.5 seroresponse rate in the evaluable immunogenicity population with or without prior evidence of infection was assessed in study participants >55 years of age and compared to study participants from C4591031 Substudy E (Table 6). The noninferiority criterion of the difference in seroresponse rates was met for participants >55 years of age as the LB of the 95% CI was 19.59%, which was greater than the noninferiority threshold of -5%. Difference in seroresponse rates for Omicron BA.4/BA.5 reported for participants in the evaluable immunogenicity population without prior evidence of infection was similar to that reported in Table 6.

Table 6. Adjusted Difference in Seroresponse Percentages – 1 Month Postvaccination, All Participants – Evaluable Immunogenicity Population – Study C4591031 and Combined Cohorts 2 and 3 in Study C4591044

SARS-CoV-2 neutralization assay	C4591044 BNT162b2 Bivalent (18-55 YOA) N=294 n (%) [95% CI]	C4591044 BNT162b2 Bivalent (>55 YOA) N=282 n (%) [95% CI]	C4591031 BNT162b2 Substudy E (>55 YOA) N=273 n (%) [95% CI]	C4591044 (>55 YOA)/ C4591031 (>55 YOA) % Difference (95% CI)	C4591044 (18-55 YOA) / C4591044 (>55 YOA) % Difference (95% CI)
Omicron BA.4/BA.5 - NT50 (titer)	180 (61.2%) [55.4, 66.8]	188 (66.7%) [60.8, 72.1]	127 (46.5%) [40.5, 52.6]	26.77 (19.59, 33.95)	-3.03 (-9.68, 3.63)

Source: Adapted from Table 39 in C4591044-interim-c2-c3-mth1-report-body.pdf submitted to STN 125742/276.0.

Omicron BA.4/BA.5 GMRs and Difference in Seroresponse rates in participants 18 to 55 years of age vs. participants >55 years of age

The noninferiority of the immune response of 30μg BNT162b2 Bivalent in participants aged 18 to 55 years was compared to 30μg BNT162b2 Bivalent in participants >55 years of age in terms of GMT and seroresponse rate. The model-based GMR was determined to be 0.98 (95% CI: 0.83, 1.16) shown in Table 5. The noninferiority criterion was met, as the LB of the 95% CI for GMR was greater than 0.67. The noninferiority criterion was also met for participants without evidence of prior infection (GMR: 1.00 (95% CI: 0.71, 1.41)).

The noninferiority criterion of the difference in seroresponse rates was met for participants 18 to 55 years of age as the LB of the 95% CI was -9.68% (Table 6), which was greater than the NI threshold of -10%.

GMT and Seroresponse for participants 12 through 17, 18 through 55, and >55 years of age in Cohort 2

The third primary objective was to describe the immune response to BNT162b2 Bivalent 30 μg or 60 μg in study participants 12-17, 18-55 and >55 years of age from Cohort 2.

Omicron BA.4/BA.5 GMTs at pre-vaccination and 1 month after study vaccination in the evaluable immunogenicity population with or without evidence of infection are presented in Table 7. Omicron BA.4/BA.5 GMTs were higher in participants 12 through 17 years of age in the BNT162b2 Bivalent 30 μg (Group 1) compared with other age and vaccine groups at both pre-vaccination and 1 month after vaccination. GMTs were similar in participants 18 through 55 and >55 years of age who received BNT162b2 Bivalent at either dose. GMTs were generally higher in the BNT162b2 Bivalent 60-μg group compared with that in the 30-μg group. No hypothesis testing was prespecified for this analysis.

Table 7. Geometric Mean Titers up to 1 Month Postvaccination – Evaluable Immunogenicity Population – Cohort 2 in Study C4591044

SARS-CoV-2 neutralization assay (NT50)	Group 1 12-17 YOA 30µg GMT (95 CI%)	Group 2 18-55 YOA 30µg GMT (95 CI%)	Group 3 18-55 YOA 60µg GMT (95 CI%)	Group 4 >55 YOA 30µg GMT (95 CI%)	Group 5 >55 YOA 60µg GMT (95 CI%)
Omicron BA.4/BA.5	-	-	-	-	-
Pre-vax	1105.8 (835.1, 1464.3)	338.3 (238.1, 480.7)	607.0 (433.2, 850.6)	301.9 (215.6, 422.8)	582.4 (397.6, 853.1)
One Month	8212.8 (6807.3, 9908.7)	2839.0 (2150.0, 3748.8)	5454.2 (4292.2, 6930.8)	3019.8 (2327.5, 3918.0)	5472.8 (3930.9, 7619.6)
Reference strain	-	-	-	-	-
Pre-vax	6863.3 (5587.8, 8430.1)	2349.0 (1693.4, 3258.4)	4287.4 (3245.6, 5663.8)	2643.1 (1990.8, 3509.1)	4324.8 (3099.0, 6035.4)
One Month	23641.3 (20473.1, 27299.8)	11919.3 (9839.1, 14439.3)	18614.7 (15754.1, 21994.7)	12103.8 (9992.0, 14662.0)	22982.3 (18524.3, 28513.3)

Source: Adapted from Table 14.20 in C4591044-interim-c2-c3-mth1-report-body.pdf submitted to STN 125742/276.0.

6.1.11.2 Analyses of Secondary Endpoints

The secondary immunogenicity objective was to assess the noninferiority of the anti–reference-strain immune response induced by BNT162b2 Bivalent 30 µg in the >55-age group relative to the anti-reference-strain immune response elicited by BNT162b2 30 µg in the >55-age group.

In the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination, model-based GMR of reference strain neutralization titers for participants >55 years of age in the BNT162b2 Bivalent 30-µg group to C4591031 Substudy E participants >55 years of age in the BNT162b2 30 µg was 1.38 (95% CI: 1.22, 1.56) as shown in Table 5. The noninferiority criteria of anti-reference-strain immune response of BNT162b2 Bivalent 30 µg to BNT162b2 30 µg in the >55-year age group were met, as the lower bound of the 95% CI for GMR was >0.67 and the point estimate was ≥0.8.

6.1.11.3 Subpopulation Analyses

Subpopulation analysis by gender and age were conducted. Results were generally similar between male and female participants. No subgroup analysis by race or ethnicity was conducted.

6.1.11.4 Exploratory and Post Hoc Analyses

GMTs of antibodies against some new variants were evaluated among a subset of Cohort 2 subjects >55 years of age. Within both baseline positive or baseline negative groups, Omicron variants BA.4.6, BA.2.75.2, BQ.1.1, and XBB neutralizing GMTs at 1 month post-dose were numerically higher for participants >55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared with the BNT162b2 30-µg group. GMTs at pre-dose and 1 month post-dose were numerically higher for participants in both vaccine groups in the evaluable immunogenicity population who were baseline positive compared with those who were baseline negative.

6.1.12 Safety Analyses

Available safety data as of October 12, 2022 for Cohort 2 (Group 1, Group 2 and Group 4) and October 31, 2022 for Cohort 3 were summarized.

Table 8 summarizes the local reactions and systemic events recorded in the e-diary for 7 days after vaccination for all participants 12 through 17 (n=107), 18 through 55 (n=313) and >55 years of age (n=306) who received a 30-µg booster dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5). Pain at the injection site was the most frequently reported local reaction within 7 days after booster dose (by 70.1%, 76.1% and 57.1% of the participants 12 through 17, 18 through 55 and >55 years of age, respectively). Swelling and redness at the injection site were reported less frequently. Most local reactions were mild or moderate in severity. A severe local reaction was reported by 1 participant each in the 12 through 17 and >55 years of age groups (pain at the injection site). No Grade 4 local reactions were reported in any group.

Fatigue was the most frequently reported systemic event within 7 days after booster dose (by 67.3%, 61.2% and 38.5% of the participants 12 through 17, 18 through 55 and >55 years of age, respectively), followed by headache, muscle pain, chills and less frequently by joint pain, diarrhea, or fever. Most systemic events were mild or moderate in severity. Among participants 18 through 55 years of age, severe systemic events of fatigue (n=6), headache (n=2), chills (n=2), and diarrhea (n=1) were reported. Among participants >55 years of age, severe systemic events of fatigue (n=4) and chills (n=1) were reported. No Grade 4 systemic events were reported in any group.

The incidences of solicited adverse reactions were generally higher in participants 12 through 17 and 18 through 55 years of age compared to participants >55 years of age.

Table 8. Solicited Reactions – Cohorts 2 and 3 in Study C4591044

Solicited Adverse Reaction	Cohort 2/ Group 1 12-17 YOA N[a]=107	Combined Cohort 2/3 18-55 YOA N[a]=310	Combined Cohort 2/3 >55 YOA N[a]=301
Local Reactions	-	-	-
Redness	-	-	-
Any	6 (5.6)	20 (6.5)	12 (4.0)
Severe	0 (0)	0	0
Pain	-	-	-
Any	75 (70.1)	236 (76.1)	172 (57.1)
Severe	1 (0.9)	0	1 (0.3)
Swelling	-	-	-
Any	8 (7.5)	22 (7.1)	8 (2.7)
Severe	0 (0)	0	0
Systemic Reactions	-	-	-
Fever	-	-	-
Any	10 (9.3)	15 (4.9)	13 (4.3)
>40.0°C	0	0	0
Fatigue	-	-	-
Any	72 (67.3)	189 (61.2)	116 (38.5)
Severe	0	6 (1.9)	4 (1.3)
Headache	-	-	-
Any	54 (50.5)	144 (46.6)	92 (30.7)
Severe	0	2 (0.6)	0
Chills	-	-	-
Any	25 (23.4)	68 (22.0)	36 (12.0)
Severe	0	2 (0.6)	1 (0.3)
Vomiting	-	-	-
Any	3 (2.8)	6 (1.9)	2 (0.7)
Severe	0	0	0
Diarrhea	-	-	-
Any	7 (6.5)	33 (10.7)	29 (9.6)
Severe	0	1 (0.3)	0
New or worsened muscle pain	-	-	-
Any	28 (26.2)	94 (30.4)	54 (18.0)
Severe	0	0	0
New or worsened joint pain	-	-	-
Any	13 (12.1)	46 (14.9)	36 (12.0)
Severe	0	0	0

a. N = number of participants reporting at least 1 yes or no response for the specified reaction after the study vaccination.
Source: Adapted from Tables 14.41, 14.48, 14.69 and 14.76 in C4591044-interim-c2-c3-mth1-report-body.pdf submitted to STN 125742/276.0.

Eight (7.5%) participants 12 through 17 years of age reported at least one unsolicited adverse event within a month of vaccination in Cohort 2/Group 1. Forty study participants reported at least one unsolicited adverse event within a month of vaccination in the combined Cohort 2/3 data (6.1% and 6.9% of the participants 18 through 55 and >55 years of age, respectively). The most frequently reported AE was lymphadenopathy in 5 (1.6%) participants in the 18 through 55 years of age group and 1 (0.3%) participant in the >55 years of age group.

One (0.3%) Serious AE (SAE) was reported by a participant 18 through 55 years of age and 2 (0.7%) SAEs were reported by participants >55 years of age. No life-threatening AEs, withdrawals due to AEs, or deaths were reported.

6.2 Trial #2: BNT162-17

Study BNT162-17 was a Phase 2 study to evaluate the safety and immunogenicity of monovalent and bivalent vaccines in healthy participants.

6.2.1 Objectives

The applicant reevaluated data from this study Part B to evaluate immunogenicity of a single dose of variant (Alpha/Delta)-modified bivalent BNT162b2 (B.1.1.7 + B.1.617.2) in vaccine naïve seropositive individuals. Only immunogenicity data were submitted and reviewed.

Primary objective:
To demonstrate noninferiority of immune response against reference strain at 3 weeks after 1 dose of BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve participants with evidence of prior infection to the immune response 1 month after 2 doses of original BNT162b2 in participants without evidence of infection from the Phase 3 trial C4591001 in terms of GMT and seroresponse rate.

Secondary objective:
To compare the immune response against Alpha, Delta and Omicron BA.5 variants 3 weeks after 1 dose of BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve participants with evidence of prior infection to the immune response 1 month after 1 booster dose (or 2 doses) of BNT162b2 (B.1.1.7 + B.1.617.2) in BNT162b2-experienced participants without evidence of infection.

6.2.2 Design Overview

The study consisted of three parts, Part A, Part B, and Part C, and evaluated the safety and immunogenicity of BNT162b2-based vaccines against variant strains. Part B consisted of participants ≥18 to ≤85 years old in 3 cohorts (Cohort 1, Cohort 4, and Cohort 6), with approximately 375 participants in each cohort. For this sBLA, clinical data from a subset of Part B (Cohorts 1 and 6) were submitted:

- Cohort 1 enrolled participants from Study C4591001 who received 2 doses of 30 μg original BNT162b2. At least 6 months after the second BNT162b2 dose,

participants received an additional dose (i.e., Dose 3) of 30 µg of the variant (Alpha/Delta)-modified bivalent BNT162b2 (B.1.1.7 + B.1.617.2) vaccine on Day 1.

- Cohort 6 enrolled participants who had not received any vaccine against COVID-19. Participants received 3 doses of 30 µg of the variant (Alpha/Delta)-modified bivalent BNT162b2 (B.1.1.7 + B.1.617.2) vaccine: 1 dose each on Day 1 and Day 21, and the third dose approximately 6 months after the second dose.

Data from Cohort 6 were used to evaluate the immunogenicity of the first dose of investigational variant (Alpha/Delta)-modified BNT162b2 bivalent (B.1.1.7 + B1.617.2) vaccine in COVID-19 vaccine-naïve participants who had evidence of prior SARS-CoV-2 infection (seropositive).

To bridge to the efficacy demonstrated with the original BNT162b2 vaccine in COVID-19 vaccine-naïve and SARS-CoV-2 seropositive individuals receiving a single dose of BNT162b2, neutralizing titers against the SARS-CoV-2 reference strain were compared between vaccine-naïve SARS-CoV-2 seropositive participants after 1 dose of BNT162b2 (B.1.1.7 + B.1.617.2) and vaccine-naïve seronegative participants after 2 doses of original BNT162b2 (from Study C4591001). In addition, neutralizing titers against the vaccine-encoded strains, i.e. Alpha and Delta, and the more contemporaneous B.1.1.529.5 (Omicron BA.5) were also assessed.

Reviewer's Comment:
The immunogenicity analyses on Cohort 6 were intended to fill the evidence gap for the use of a single dose of BNT162b2 in seropositive individuals 12 years of age and older who had not been previously vaccinated with a COVID-19 vaccine. The applicant stated that although the Alpha (B.1.1.7) and Delta (B.1.617.2) variants were no longer epidemiologically relevant, experience with variant-modified versions of BNT162b2 was relevant because all have the same lipid nanoparticle (LNP) formulation and RNA components except that the RNAs differ slightly in their encoded open reading frame (ORF).

6.2.3 Population

Part B enrolled healthy participants ≥18 to ≤85 years old. For Cohort 1, prior enrollment and dosing in the C4591001 trial was mandatory. Participants should have not experienced COVID-19 based on medical history. Cohort 6 subjects were COVID-19 vaccine-naïve and had not experienced COVID-19 based on their medical history.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Intramuscular injection of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2).

6.2.5 Directions for Use

Please refer to Dr. Adam Spanier's clinical review memo.

6.2.6 Sites and Centers

This study was conducted at 11 sites in South Africa, 10 sites in the United States, and 5 sites in Turkey.

6.2.7 Surveillance/Monitoring

Please refer to Adam Spanier's clinical review memo.

6.2.8 Endpoints and Criteria for Study Success

Primary endpoint: NTs against reference strain
Secondary endpoint: NTs against specific variants of concern (VOCs) (B.1.1.7, B.1.617.2, B.1.1.529.5 [Omicron BA.5])

6.2.9 Statistical Considerations & Statistical Analysis Plan

Success criteria and statistical methods for the primary immunogenicity analysis
Non-inferiority of immune response against reference strain 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in Cohort 6 subjects with evidence of prior infection vs. immune response against reference strain 1 month after two doses of BNT162b2 in subjects without evidence of infection was assessed using a 1.5-fold NI margin for GMR and 10% NI margin for difference in seroresponse rates.

Model-based GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on the analysis of logarithmically transformed neutralizing titers using a linear regression model with terms for age, sex, and group. Unadjusted GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers and the corresponding CIs (based on the Student's t distribution).

Seroresponse was defined as achieving a ≥4-fold rise from baseline. If the baseline measurement was below the LLOQ, a postvaccination assay result of ≥4 × LLOQ was considered a seroresponse. The adjusted difference in proportions was estimated using minimum risk weights and stratified by sex and age group (18 to 55 years, 56 to 85 years). The 95% CI was calculated using Newcombe method stratified by sex and age group with minimum risk weights for the difference in proportions.

Since this was an ad hoc analysis, the sample size was not based on statistical considerations.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Reference Strain Neutralization Immunogenicity Population
A total of 276 participants were included in each of the 2 groups. The immunogenicity analysis set included 262 (94.9%) participants in the BNT162-17 bivalent BNT162b2 group and 275 (99.6%) in the C4591001 original BNT162b2 group. Fourteen (5.1%) participants in the BNT162-17 bivalent BNT162b2 group and 1 (0.4%) participant in the

C4591001 original BNT162b2 group were excluded from the immunogenicity analysis set for not having at least 1 valid and determinate immunogenicity result within the specified window after study vaccination. The demographic characteristics of the immunogenicity analysis set are presented in Table 9. In the BNT162-17 bivalent BNT162b2 group, 64.5% were Black or African American, 96.6% were from South Africa, and 97.3% were of non-Hispanic/non-Latino ethnicity. In the C4591001 original BNT162b2 group, 83.6% were White, 70.5% were from the USA, and 69.8% were of non-Hispanic/non-Latino ethnicity. Other demographic characteristics, including sex and age, were generally balanced between the 2 groups.

Variant (Alpha, Delta, and Omicron BA.5) Strain Immunogenicity Population
Variant neutralization data were summarized for a subset of 149 participants with evidence of prior infection in Part B Cohort 6 (hereafter referred to as Cohort 6 with evidence of prior infection group) . Comparator subsets of 19 participants without evidence of infection from Part B Cohort 6 (hereafter referred to as Cohort 6 without evidence of infection group) and 136 participants without evidence of infection from Part B Cohort 1 (hereafter referred to as Cohort 1 without evidence of infection group) were also included in variant strain immunogenicity analyses. The immunogenicity analysis set included 142 (95.3%) participants in the Cohort 6 with evidence of prior infection group, 17 (89.5%) participants in the Cohort 6 without evidence of infection group, and 136 (100.0%) participants in the Cohort 1 without evidence of infection group.

The demographic characteristics of the immunogenicity analysis set are summarized in Table 10. The majority of participants in the Cohort 6 with evidence of prior infection group were Black or African American, from South Africa, and of non-Hispanic/non-Latino ethnicity; the median (min, max) age at first study vaccination was 38.5 (18, 79) years old. The majority of participants in the Cohort 1 without evidence of infection group were White, half of the participants were from USA, and most were of non-Hispanic/non-Latino ethnicity; the median (min, max) age at first study vaccination was 49.0 (18, 80) years old.

Table 9. Demographic Characteristics – Study BNT162-17 Part B Cohort 6 (Primary Series) and Subset of Study C4591001 (Primary Series) – Reference Strain Neutralization – Immunogenicity Analysis Set

Vaccine Group	BNT162-17 Cohort 6 BNT162b2 (B.1.1.7 + B.1.617.2) 30 µg With Evidence of Prior Infection	C4591001 BNT162b2 30 µg Without Evidence of Infection
	(N=262)	(N=275)
	n (%)	n (%)
Sex		
Male	109 (41.6)	113 (41.1)
Female	153 (58.4)	162 (58.9)
Race		
White	4 (1.5)	230 (83.6)
Black or African American	169 (64.5)	25 (9.1)
American Indian or Alaska Native	0	2 (0.7)
Asian	0	7 (2.5)
Multiracial	37 (14.1)	7 (2.5)
Not reported	0	4 (1.5)
Other	52 (19.8)	0
Ethnicity		
Hispanic/Latino	5 (1.9)	83 (30.2)
Non-Hispanic/non-Latino	255 (97.3)	192 (69.8)
Unknown	2 (0.8)	0
Country		
Argentina	0	49 (17.8)
Brazil	0	19 (6.9)
Germany	0	3 (1.1)
South Africa	253 (96.6)	8 (2.9)
Turkey	0	2 (0.7)
USA	9 (3.4)	194 (70.5)
Age (years)		
n	262	275
Mean (SD)	42.9 (16.21)	42.7 (16.08)
Median	41.0	40.0
Min, max	(18, 84)	(18, 84)
Body mass index (BMI)		
Underweight (<18.5 kg/m^2)	27 (10.3)	2 (0.7)
Normal weight (≥18.5-<25.0 kg/m^2)	110 (42.0)	108 (39.3)
Overweight (≥25.0-<30.0 kg/m^2)	57 (21.8)	74 (26.9)
Obese (≥30.0 kg/m^2)	65 (24.8)	91 (33.1)
Missing	3 (1.1)	0

Source: Adapted from Table 3 in BNT162-17-single-dose-immuno-data.pdf submitted to STN 125742/276.25.

Table 10. Demographic Characteristics – Subset of Part B Cohort 6 (Primary Series) and Cohort 1 (Booster) – Variant Neutralization – Immunogenicity Analysis Set

	Cohort 6: With Evidence of Prior Infection (N=142) n (%)	Cohort 6: Without Evidence of Prior Infection (N=17) n (%)	Cohort 1: Without Evidence of Prior Infection (N=136) n (%)
Sex			
Male	68 (47.9)	11 (64.7)	75 (55.1)
Female	74 (52.1)	6 (35.3)	61 (44.9)
Race			
White	1 (0.7)	4 (23.5)	114 (83.8)
Black or African American	96 (67.6)	9 (52.9)	7 (5.1)
American Indian or Alaska Native	0	0	1 (0.7)
Asian	0	0	5 (3.7)
Multiracial	21 (14.8)	1 (5.9)	9 (6.6)
Other	24 (16.9)	3 (17.6)	0
Ethnicity			
Hispanic/Latino	3 (2.1)	3 (17.6)	15 (11.0)
Non-Hispanic/non-Latino	138 (97.2)	14 (82.4)	120 (88.2)
Not reported	0	0	1 (0.7)
Unknown	1 (0.7)	0	0
Country			
South Africa	137 (96.5)	9 (52.9)	19 (14.0)
Turkey	0	0	49 (36.0)
USA	5 (3.5)	8 (47.1)	68 (50.0)
Age (years)			
n	142	17	136
Mean (SD)	42.3 (16.72)	55.2 (13.92)	47.6 (15.43)
Median	38.5	59.0	49.0
Min, max	(18, 79)	(24, 78)	(18, 80)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	11 (7.7)	2 (11.8)	3 (2.2)
Normal weight (≥18.5-<25.0 kg/m^2)	67 (47.2)	9 (52.9)	41 (30.1)
Overweight (≥25.0-<30.0 kg/m^2)	33 (23.2)	4 (23.5)	41 (30.1)
Obese (≥30.0 kg/m^2)	31 (21.8)	2 (11.8)	48 (35.3)
Missing	0	0	3 (2.2)

Source: Adapted from Table 10 in BNT162-17-single-dose-immuno-data.pdf submitted to STN 125742/276.25.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Endpoints

In the immunogenicity analysis set, model-based GMR of reference strain neutralizing titer in the BNT162-17 bivalent BNT162b2 group at 3W PD1 to that in the C4591001 original BNT162b2 group at 1M PD2 was 13.12 (95% CI: 11.14, 15.45) as shown in Table 11. The noninferiority criterion of reference strain immune response in terms of GMT for the BNT162-17 bivalent BNT162b2 group was met, as the lower bound of the 95% CI for GMR was >0.67.

Table 11. Model-Based Geometric Mean Ratios – Study BNT162-17 Part B Cohort 6 (Primary Series) and Subset of Study C4591001 (Primary Series) – Reference Strain Neutralization – Immunogenicity Analysis Set

	BNT162-17 Cohort 6 BNT162b2 (B.1.1.7 + B.1.617.2) 30 µg With Evidence of Prior Infection	**C4591001 BNT162b2 30 µg Without Evidence of Infection**	
SARS-CoV-2 neutralization assay – NT50	**N GMT (95% CI)**	**N GMT (95% CI)**	**GMR (95% CI)**
Reference (original) strain	262 17404.2 (15485.1, 19561.1)	275 1328.1 (1183.1, 1491.0)	13.12 (11.14, 15.45)

Source: Adapted from Table 4 in BNT162-17-single-dose-immuno-data.pdf submitted to STN 125742/276.25.

Reviewer's Comments:

1. *The model-based GMTs for BNT162-17 bivalent group and C4591001 original BNT162b2 group as presented in Table 11 appeared to be unadjusted GMTs. I calculated the model-based GMTs to be 17183.5 and 1309.9, respectively, for these two groups. The model-based GMR in the last column matched my calculation.*
2. *The imbalance in demographic characteristics between these two groups was large which could limit the interpretation of the analysis result. For example, BNT162-17 Cohort 6 subjects were mostly (96.6%) from South African, while only 2.9% of C4591001 subjects were from South African.*
3. *I included baseline titer as an additional covariate in the linear regression model for a sensitivity analysis. The model-based GMR of NT in the BNT162-17 bivalent BNT162b2 group to that in the C4591001 original BNT162b2 group was 5.59 (95% CI: 4.44, 7.03).*

In the immunogenicity analysis set, 85.8% in the BNT162-17 bivalent BNT162b2 group at 3W PD1 and 90.5% in the C4591001 original BNT162b2 group at 1M PD2 achieved seroresponse to the reference strain (Table 12). The adjusted difference in seroresponse rates between the BNT162-17 bivalent group and the C4591001 original BNT162b2

group was -4.55% (95% CI: -10.04%, 0.83%). The noninferiority criterion of reference strain based on seroresponse rate for the BNT162-17 bivalent BNT162b2 group was not met, as the lower bound of the 95% CI for the difference in seroresponse rates for reference strain was 0.04% lower than the noninferiority threshold of -10%.

Table 12. Difference in Percentages of Participants With Seroresponse– Study BNT162-17 Part B Cohort 6 (Primary Series) and Subset of Study C4591001 (Primary Series) – Reference Strain Neutralization – Immunogenicity Analysis Set

	BNT162-17 Cohort 6 BNT162b2 bivalent 30 µg With Evidence of Prior Infection	**C4591001 BNT162b2 30 µg Without Evidence of Infection**	
SARS-CoV-2 neutralization assay – NT50	**N n (%) (95% CI)**	**N n (%) (95% CI)**	**Difference % (95% CI)**
Reference (original) strain	260 223 (85.8) (80.9, 89.8)	275 249 (90.5) (86.5, 93.7)	-4.55 (-10.04, 0.83)

Source: Adapted from Table 5 in BNT162-17-single-dose-immuno-data.pdf submitted to STN 125742/276.25.

Reviewer's Comment:
The BNT162-17 bivalent group had substantially higher pre-vaccination titers than the C4591001 original BNT162b2 group due to prior SARS-CoV-2 infection (GMTs were 548.1 and 45.1 for the two groups, respectively), which requires much higher post-vaccination titers to achieve seroresponse.

6.2.11.2 Analyses of Secondary Endpoints

In the immunogenicity analysis set, the observed GMTs of Alpha, Delta, and Omicron BA.5 neutralizing titers at 3 weeks after a single dose in Cohort 6 participants with evidence of prior infection were numerically higher than those at 1 month after 2 doses in Cohort 6 participants without evidence of infection and at 1 month after the third dose in Cohort 1 participants without evidence of infection (Table 13).

Table 13. Model-Based Geometric Mean Ratios – Subset of Part B Cohort 6 (Primary Series) and Cohort 1 (Booster) – Variant Neutralization – Immunogenicity Analysis Set

	Cohort 6 With Evidence of Prior Infection 3W PD1	Cohort 6 Without Evidence of Infection 1M PD2	Cohort 1 Without Evidence of Infection 1M PD3
SARS-CoV-2 neutralization assay - NT50	**n GMT (95% CI)**	**n GMT (95% CI)**	**n GMT (95% CI)**
Alpha (B.1.1.7)	142 1045.3 (853.1, 1280.8)	17 180.8 (91.8, 356.3)	136 749.5 (621.1, 904.6)
Delta (B.1.617.2)	142 859.9 (693.4, 1066.4)	17 62.6 (30.9, 127.0)	136 466.6 (401.8, 541.9)
Omicron BA.5 (B.1.1.529.5)	142 229.3 (191.7, 274.4)	17 10.2 (5.7, 18.3)	136 80.8 (66.9, 97.6)

Source: Adapted from Table 11 in BNT162-17-single-dose-immuno-data.pdf submitted to STN 125742/276.25.

Reviewer's Comment:
The distribution of demographics of the three groups were imbalanced (as shown in Table 10), which may confound the immunogenicity results. Hence, the immunogenicity analysis was considered to be descriptive in nature and the GMR results across groups are not shown in Table 13.

In the immunogenicity analysis set, the observed seroresponse rates against Alpha, Delta, and Omicron BA.5 at 3 weeks after a single dose of vaccine in Cohort 6 vaccine-naïve participants with evidence of prior infection were >87% (Table 14). Comparing with Cohort 6 without evidence of infection group at 1 month after 2 doses, higher rates of seroresponse to all three variants were observed in Cohort 6 with evidence of prior infection group, especially for Delta and Omicron BA.5. Comparing with Cohort 1 without evidence of infection group at 1 month after the third dose, the observed seroresponse rates in Cohort 6 with evidence of prior infection group were lower for Alpha and Delta but slightly higher for Omicron BA.5.

Table 14. Adjusted Difference in Percentages of Participants With Seroresponse – Subset of Part B Cohort 6 (Primary Series) and Cohort 1 (Booster) – Variant Neutralization – Immunogenicity Analysis Set

	Cohort 6 With Evidence of Prior Infection 3W PD1	Cohort 6 Without Evidence of Infection 1M PD2	Cohort 1 Without Evidence of Infection 1M PD3
SARS-CoV-2 neutralization assay – NT50	**N n (%) (95% CI)**	**N n[d] (%) (95% CI)**	**N n (%) (95% CI)**
Alpha (B.1.1.7)	142 124 (87.3) (80.7, 92.3)	17 13 (76.5) (50.1, 93.2)	136 132 (97.1) (92.6, 99.2)
Delta (B.1.617.2)	142 127 (89.4) (83.2, 94.0)	17 10 (58.8) (32.9, 81.6)	136 131 (96.3) (91.6, 98.8)
Omicron BA.5 (B.1.1.529.5)	142 124 (87.3) (80.7, 92.3)	17 2 (11.8) (1.5, 36.4)	136 109 (80.1) (72.4, 86.5)

Source: Adapted from Table 12 in BNT162-17-single-dose-immuno-data.pdf submitted to STN 125742/276.25.

6.2.11.3 Subpopulation Analyses

Subgroup analyses by age and BMI generally followed a similar trend as the overall results (data not shown).

6.2.11.4 Exploratory and Post Hoc Analyses

No exploratory and post-hoc analyses were considered.

6.2.12 Safety Analyses

No safety analyses in this study were considered for this sBLA.

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated summary of efficacy was submitted.

8. INTEGRATED OVERVIEW OF SAFETY

No integrated summary of safety was submitted.

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues.

10. CONCLUSIONS

The pre-specified success criteria for the primary immunogenicity endpoints were met in

both Study C4591044 and Study BNT162-17 except for the seroresponse rate endpoint in Study BNT162-17. No significant safety concerns were identified in the study populations. I defer to the clinical reviewer on the acceptability of the totality of the immunogenicity and safety data regarding single dose use of the BNT162b2 (2023-2024 Formula) vaccine in individuals 12 years of age and older regardless of previous vaccination status.