Application Type	BLA Supplement
STN	125742/45
CBER Received Date	December 16, 2021
PDUFA Goal Date	June 17, 2022
Division / Office	DVRPA/OVRR
Committee Chair	Ramachandra Naik
Clinical Reviewer(s)	Susan Wollersheim
Project Manager	Michael Smith; Laura Gottschalk
Priority Review	Yes
Reviewer Name	Ye Yang, Mathematical Statistician, DB/VEB
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Concurring Reviewer, DB/VEB
Supervisory Concurrence	Tsai-Lien Lin, Branch Chief, DB/VEB
Applicant	BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)
Established Name	COVID-19 Vaccine, mRNA
(Proposed) Trade Name	COMIRNATY
Dosage Form(s) and Route(s) of Administration	Injectable Suspension, Intramuscular
Dosing Regimen	Two 0.3 mL doses, three weeks apart
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 through 15 years of age

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GLOSSARY

ADaM	Analysis Data Model
AE	Adverse Event
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
EUA	Emergency Use Authorization
GMT	Geometric Mean Titer
GMR	Geometric Mean Titer Ratio
NAAT	Nucleic Acid Amplification Test
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SDTM	Study Data Tabulation model
SRR	Seroresponse Rate
VE	Vaccine Efficacy

1. Executive Summary

The Pfizer-BioNTech COVID-19 Vaccine (BNT162b2, COMIRNATY) was licensed on August 23, 2021 for active immunization to prevent Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals ≥16 years of age. Pfizer submitted a Biologics License Application Supplement (sBLA; STN 125742/45) on December 16, 2021 to seek licensure of COMIRNATY for use in individuals 12 through 15 years of age. The sBLA is supported by data from Study C4591001. This statistical review focuses on the efficacy, immunogenicity, and safety data from adolescents 12 through 15 years of age in the Phase 3 part of Study C4591001 collected up to the September 2, 2021 data cutoff.

Study C4591001 is an ongoing, randomized, placebo-controlled, observer-blinded Phase 1/2/3 study being conducted in the United States, Argentina, Brazil, Germany, South Africa, and Turkey among participants ≥12 years of age. Adolescents 12 through 15 years of age, included in the Phase 3 portion of the study under a protocol amendment, were enrolled at selected sites in the United States, where 2,264 participants were randomized 1:1 to receive two doses of BNT162b2 or placebo 21 days apart. Immunogenicity was assessed at 1 month after Dose 2. A random sample of 280 adolescents was selected to support immunobridging to a random sample of 280 young adults 16 to 25 years of age from the same study. Supplementary to immunobridging, adolescents were surveilled for potential cases of COVID-19.

The prespecified immunobridging success criterion comparing 12 to 15 year-old geometric mean neutralizing titers (GMTs) to 16 to 25 year-old GMTs from Study C4591001 was met (GMT ratio [GMR]=1.77; 95% Confidence Interval [CI]: 1.50 to 2.09). High efficacy against protocol-defined COVID-19 was observed among participants in the Evaluable Efficacy Population without evidence of prior SARS-CoV-2 infection starting at 7 days post Dose 2 (Vaccine Efficacy [VE]=100%; 95% CI: 86.8% to 100%) and among participants in the Dose 1 All-Available Efficacy Population starting after Dose 1 (VE=94.0%; 95% CI: 81.3% to 98.8%). The lack of severe COVID-19 cases observed precludes assessment of efficacy against severe disease in this population.

The frequency and severity of local and systemic reactions were generally higher among BNT162b2 recipients than among placebo recipients after either dose. The most commonly reported adverse reactions were injection site pain, fatigue, and headache. There was no notable difference in the frequency of any unsolicited adverse event (AE) between arms during blinded follow-up, while a higher percentage of BNT162b2 recipients reported any serious AE (SAE; 0.9%) compared to placebo recipients (0.2%). Of note, no SAE reported during blinded follow-up was considered by the investigator to be related to the study intervention. No participants died as of the September 2, 2021 cutoff. One SAE of myocarditis was reported in a 15-year-old male participant 2 days after receiving the second crossover dose of BNT162b2. One SAE of appendicitis in a 12-year-old female participant was reported 3 days after the second crossover dose and was considered by the investigator to be related to the study vaccination.

Overall, the clinical data support the effectiveness of BNT162b2. While there is some reactogenicity associated with BNT162b2, the majority of solicited adverse reactions were mild or moderate in severity and of short duration. I defer to the clinical reviewer, Dr. Susan Wollersheim, on the overall safety conclusion for BNT162b2.

2. Clinical and Regulatory Background

The Pfizer-BioNTech COVID-19 Vaccine (BNT162b2, COMIRNATY) was authorized under an Emergency Use Authorization (EUA) on December 11, 2020 for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥16 years of age, which was amended to include individuals 12 through 15 years of age on May 10, 2021. COMIRNATY was licensed for use in individuals ≥16 years of age on August 23, 2021. Pfizer submitted an sBLA (STN 125742/45) on December 16, 2021 to seek licensure of COMIRNATY for use in individuals 12 through 15 years of age.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to Kanaeko Ravenell's Bioresearch Monitoring inspections review memo.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to reviews of other review disciplines.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This statistical review focuses on the efficacy, immunogenicity, and safety data from adolescents 12 to 15 years of age in the Phase 3 part of Study C4591001 collected up to the September 2, 2021 data cutoff.

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

The following documents submitted to the sBLA are reviewed:

STN 125742/45:

1. Amendment 0 (submitted on 12/16/2021)
    - Module 2. Common Technical Document Summaries
    - Module 5. Clinical Study Reports
2. Amendment 2 (submitted on 2/2/2022)

- Module 1. Administrative Information and Prescribing Information

3. Amendment 4 (submitted on 3/11/2021)
   - Module 1. Administrative Information and Prescribing Information
4. Amendment 7 (submitted on 3/18/2021)
   - Module 1. Administrative Information and Prescribing Information

5.3 Table of Studies/Clinical Trials

Data from one ongoing clinical study were submitted to support licensure in adolescents (Table 1). Study C4591001 is a multi-center, Phase 1/2/3, randomized, double-blinded, placebo-controlled study to evaluate safety, immunogenicity, and efficacy of BNT162b2.

Table 1. Clinical Study Supporting Licensure in Adolescents 12 Through 15 Years of Age

Study	Description	BNT162b2 (N)	Placebo (N)	Status
C4591001	Phase 1/2/3, randomized, placebo-controlled, observer-blind study to evaluate the safety, immunogenicity, and efficacy of BNT162b2	1134 (Phase 3 adolescents only)	1130 (Phase 3 adolescents only)	Ongoing

N=number of randomized participants.
Source: Summarized by the reviewer based on information provided in Clinical Overview.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study C4591001 (Phase 3)

6.1.1 Objectives

Primary Safety Objective:

- To define the safety profile of BNT162b2 in participants 12 to 15 years of age.

Secondary Immunogenicity Objective:

- To demonstrate the noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age.

Exploratory Efficacy Objective:

- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose through the blinded follow-up period in participants without, and with and without, evidence of infection before vaccination.

Reviewer comment:

- *Demonstration of efficacy was listed as an exploratory objective as immunobridging was the basis for inferring effectiveness of BNT162b2 among adolescents.*

6.1.2 Design Overview

Study C4591001 is an ongoing, randomized, placebo-controlled, observer-blinded Phase 1/2/3 study being conducted in the United States, Argentina, Brazil, Germany, South Africa, and Turkey among participants ≥12 years of age. Adolescents 12 through 15 years of age, included in the Phase 3 portion of the study under a protocol amendment, were enrolled at selected sites in the United States, where 2,264 participants were randomized 1:1 to receive two doses of BNT162b2 or placebo 21 days apart.

Immunogenicity was assessed at 1 month after Dose 2. A sample of 280 participants was randomly selected from each age group (12 to 15 years and 16 to 25 years) to support immunobridging. Supplementary to immunobridging analyses, adolescents were surveilled for potential cases of COVID-19. Those who developed acute respiratory illness were tested for SARS-CoV-2 infection using reverse transcription-polymerase chain reaction (RT-PCR) in an illness visit. Participants originally randomized to placebo who became eligible to receive BNT162b2 were offered the opportunity to receive BNT162b2 no later than 6 months post Dose 2.

All adolescents were to record local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. Unsolicited AEs and SAEs were collected starting from Dose 1.

6.1.3 Population

The study enrolled participants ≥12 years of age who, in the judgement of the investigator, were at higher risk for acquiring COVID-19, including but not limited to use of mass transportation, relevant demographics, and frontline essential workers. The age groups considered in this review are adolescents 12 to 15 years of age and young adults 16 to 25 years of age randomly sampled to support immunobridging.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study interventions were 30µg of BNT162b2 and saline placebo.

6.1.6 Sites and Centers

A total of 29 sites in the United States enrolled adolescents in the study.

6.1.7 Surveillance/Monitoring

Please refer to Dr. Susan Wollersheim's clinical review memo.

6.1.8 Endpoints and Criteria for Study Success

The immunobridging endpoint was the neutralizing antibody titer at 28 days after Dose 2. Effectiveness of BNT162b2 among adolescents was inferred by bridging their GMT of neutralizing antibodies to the GMT from a random subset of young adults 16 to 25 years of age from the same study. Success would be declared if the lower bound of the two-sided 95% CI for the GMR, where GMR is defined as GMT of adolescents divided by GMT of young adults, was >0.67. Difference in seroresponse rates (SRRs) was evaluated

descriptively. Seroresponse was defined as a change from a baseline (pre-Dose 1) titer below the LLOQ to ≥4*LLOQ 28 days after Dose 2, or a ≥4-fold rise in titer from baseline when the baseline titer is ≥LLOQ.

Efficacy was assessed descriptively based on cases of confirmed COVID-19, defined as having a positive nucleic acid amplification test (NAAT) plus at least one of the following symptoms: fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting. Severe COVID-19 was defined as a confirmed COVID-19 plus at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

Solicited safety endpoints included the occurrence of local (redness, swelling, injection site pain) and systemic (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, joint pain) reactions within 7 days of each dose. Unsolicited safety endpoints included the occurrence of AEs and SAEs within three different risk windows: 1) Dose 1 to 1 month post Dose 2, 2) Dose 1 to 6 months post Dose 2, unblinding, or the September 2, 2021 data cutoff, whichever was earlier, and 3) unblinding to the cutoff.

6.1.9 Statistical Considerations & Statistical Analysis Plan

GMR and 95% CIs were obtained by exponentiating the difference and associated 95% CIs of the mean log-titers based on the t-distribution. The confidence interval for the SRR difference was estimated via the Miettinen-Nurminen method. The primary immunobridging analysis was based on the Evaluable Immunogenicity Population, defined as participants who: 1) received both doses of the randomized vaccine, with Dose 2 within 19 to 42 days after Dose 1, 2) had at least 1 valid and determinate immunogenicity result collected within 28 to 42 days after Dose 2, and 3) had no other important protocol deviations. In addition, for the primary analysis, participants must not have any evidence of SARS-CoV-2 infection up to 1 month after Dose 2.

VE was estimated as 1 minus the incidence rate ratio of COVID-19 relative to placebo, with associated 95% CI calculated by the Clopper-Pearson method adjusted for surveillance time. Analysis was based on the Evaluable Efficacy Population, defined as participants who received the randomized intervention within the predefined window and had no major protocol deviations up to 7 days post Dose 2, and the Dose 1 All-Available Efficacy Population, defined as all randomized participants who received at least 1 dose of the intervention. Participants were analyzed according to the intervention randomized.

VE in the Evaluable Efficacy Population was descriptively presented among participants: 1) without evidence of SARS-CoV-2 infection up to 7 days post Dose 2, and 2) with or without evidence of prior infection.

Solicited safety analyses were based on participants who received at least one dose of the study intervention and responded yes or no to any reaction within 7 days of each dose. Unsolicited safety analyses were based the Safety Population, defined as all participants who received at least 1 dose of study intervention, analyzed according to the intervention received. Safety endpoints were summarized descriptively.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 2 shows the disposition of randomized adolescents 12 to 15 years of age. A total of 2,264 adolescents were randomized. The percentages of participants who received each dose were similar between the vaccine and placebo groups. In addition, 280 participants 12 to 15 years old and 280 participants 16 to 25 years old were selected for immunobridging, of which 208 (74%) and 190 (68%), respectively, had a determinate immunogenicity result available after Dose 2. The lower number of participants with an available immunogenicity result, noted by the Applicant on March 15, 2021, was due to an insufficient supply of a critical assay reagent leading to a halt to laboratory testing. A total of 190 (68%) and 170 (61%) participants, respectively, were included in the Evaluable Immunogenicity Population without evidence of infection.

Table 2. Subject Disposition

-	**BNT162b2 n (%)**	**Placebo n (%)**	**Total n (%)**
Randomized	1134 (100)	1130 (100)	2264 (100)
Not vaccinated	3 (0.3)	1 (0.1)	4 (0.2)
Vaccinated	1131 (99.7)	1129 (99.9)	2260 (99.8)
Dose 1	1131 (99.7)	1129 (99.9)	2260 (99.8)
Dose 2	1124 (99.1)	1117 (98.8)	2241 (99.0)
Withdrawn from the study	5 (0.4)	14 (1.2)	19 (0.8)
Lost to follow-up	3 (0.3)	2 (0.2)	5 (0.2)
Withdrawal by subject	1 (0.1)	7 (0.6)	8 (0.4)
Withdrawal by parent/guardian	1 (0.1)	5 (0.4)	6 (0.3)
Dose 1 All-Available Efficacy Population	1131 (99.7)	1129 (99.9)	2260 (99.8)
Evaluable Efficacy Population	1119 (98.7)	1109 (98.1)	2228 (98.4)
Without evidence of infection	1057 (93.2)	1030 (91.2)	2087 (92.2)

Source: Adapted from Tables 4 and 10 of Interim Clinical Study Report.

6.1.10.1.1 Demographics

Table 3 presents the demographic characteristics of the adolescent Safety Population. Demographic characteristics were generally similar with regard to age, sex, race, ethnicity, and baseline SARS-CoV-2 serostatus between participants who received BNT162b2 and those who received placebo. Among all participants who received either

intervention, 51.0% were male, 85.5% were White, 4.8% were Black or African American, 6.3% were Asian, and 0.3% were American Indian or Alaska Native. Demographic characteristics in the Evaluable Efficacy Population were generally similar to those in the Safety Population.

Table 3. Demographics Characteristics of the Safety Population

-	**BNT162b2 N=1131 n (%)**	**Placebo N=1129 n (%)**	**Total N=2260 n (%)**
Sex	-	-	-
Male	567 (50.1)	585 (51.8)	1152 (51.0)
Female	564 (49.9)	544 (48.2)	1108 (49.0)
Race	-	-	-
White	970 (85.8)	962 (85.2)	1932 (85.5)
Black/African-American	52 (4.6)	57 (5.0)	109 (4.8)
American Indian/Alaskan Native	4 (0.4)	3 (0.3)	7 (0.3)
Asian	72 (6.4)	71 (6.3)	143 (6.3)
Native Hawaiian/Other Pacific Islander	3 (0.3)	0	3 (0.1)
Multiracial	24 (2.1)	29 (2.6)	53 (2.3)
Not Reported	6 (0.5)	7 (0.6)	13 (0.6)
Ethnicity	-	-	-
Hispanic/Latino	132 (11.7)	130 (11.5)	262 (11.6)
Non-Hispanic/Non-Latino	997 (88.2)	996 (88.2)	1993 (88.2)
Not Reported	2 (0.2)	3 (0.3)	5 (0.2)
Age (years)	-	-	-
Mean (Standard Deviation)	13.6 (1.1)	13.6 (1.1)	13.6 (1.1)
Median (Minimum, Maximum)	14.0 (12, 15)	14.0 (12, 15)	14.0 (12, 15)
Baseline SARS-CoV-2 status	-	-	-
Positive	46 (4.1)	50 (4.4)	96 (4.2)
Negative	1083 (95.8)	1078 (95.5)	2161 (95.6)
Missing	2 (0.2)	1 (0.1)	3 (0.1)

Source: Table 11 of Interim Clinical Study Report.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Immunogenicity Endpoints

Table 4 presents the immunobridging analysis of GMR at 28 days after Dose 2 in the Evaluable Immunogenicity Population without evidence of SARS-CoV-2 infection up to 1 month post Dose 2. The GMR comparing 12 to 15 year-old GMTs to 16 to 25 year-old GMTs was 1.77 (95% CI: 1.50 to 2.09), meeting the prespecified success criterion.

Table 4. Geometric Mean Titer Ratio – Evaluable Immunogenicity Population

Group	**GMT (95% CI) 12-15 Years of Age N=190**	**GMT (95% CI) 16-25 Years of Age N=170**	**GMR (95% CI) 12-15 Years/16-25 Years**
BNT162b2	1253.6 (1117.7, 1406.1)	708.1 (625.9, 801.1)	1.77 (1.50, 2.09)

N=number of participants with available titer at 1 month after Dose 2.
Source: Summarized by the reviewer based on response to March 7, 2022 information request.

Table 5 presents descriptive analysis results for the SRR difference. Overall, 97.2% and 96.8% of adolescents and young adults, respectively, in the Evaluable Immunogenicity Population without evidence of SARS-CoV-2 infection achieved seroresponse, resulting in an SRR difference of 0.4% (95% CI: -4.2% to 5.5%).

Table 5. Seroresponse Rate Difference – Evaluable Immunogenicity Population

Group	Seroresponse n (%, 95% CI) 12-15 Years of Age N=143	Seroresponse n (%, 95% CI) 16-25 Years of Age N=124	Seroresponse % Difference (95% CI) 12-15 Years Minus 16-25 Years
BNT162b2	139 (97.2) (93.0, 99.2)	120 (96.8) (91.9, 99.1)	0.4 (-4.2, 5.5)

N=number of participants with available titer before vaccination and at 1 month after Dose 2.
n=number of participants achieving seroresponse at 1 month after Dose 2.
Source: Summarized by the reviewer based on response to March 7, 2022 information request.

Reviewer comment:

- *Analyses of GMR and SRR difference based on the same population were used to support the May 10, 2021 EUA. Of note, the applicant discovered that the assay LLOQ should have been 41 instead of* (b) (4) *in the submitted datasets. The results presented in Tables 4 and 5 reflect the updated LLOQ.*

6.1.11.2 Analyses of Efficacy Endpoints

In the Evaluable Efficacy Population without evidence of SARS-CoV-2 infection, 28 COVID-19 cases among placebo recipients and none among BNT162b2 recipients were observed during blinded follow-up from 7 days post Dose 2 to the September 2, 2021 cutoff (Table 6), resulting in a VE point estimate of 100% (95% CI: 86.8% to 100%). A similar VE was observed among participants with or without evidence of infection (VE=100%; 95% CI: 87.5% to 100%). These analyses were based on a median follow-up of 4.4 months post Dose 2.

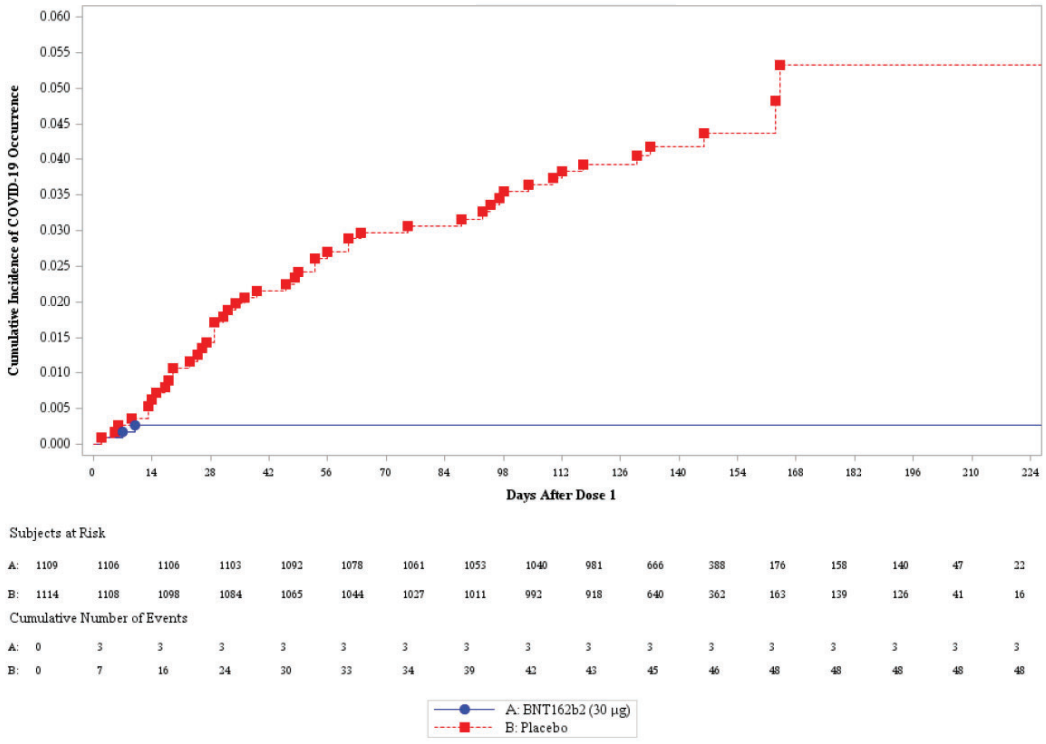
Figure 1 shows the cumulative incidence of COVID-19 in the Dose 1 All-Available Efficacy Population, where 48 cases in the placebo group and 3 cases in the BNT162b2 group were observed during blinded follow-up starting after Dose 1 (VE=94.0%; 95% CI: 81.3% to 98.8%). All 3 cases from BNT162b2 recipients occurred prior to Dose 2. No protocol-defined severe COVID-19 was observed in either group as of the cutoff.

Table 6. Efficacy by Population and Time Period

Population/Surveillance Period	BNT162b2 n (1000-py)	Placebo n (1000-py)	VE (95% CI)
Evaluable Efficacy Population without evidence of infection	N=1057	N=1030	-
≥7 days after Dose 2	0 (0.343)	28 (0.322)	100.0 (86.8, 100.0)
≥7 days to <2 months after Dose 2	0 (0.138)	15 (0.133)	100.0 (73.2, 100.0)
≥2 months to <4 months after Dose 2	0 (0.148)	10 (0.139)	100.0 (58.0, 100.0)
≥4 months after Dose 2	0 (0.057)	3 (0.050)	100.0 (-112.1, 100.0)
Evaluable Efficacy Population with or without evidence of infection	N=1119	N=1109	-
≥7 days after Dose 2	0 (0.362)	30 (0.345)	100.0 (87.5, 100.0)
≥7 days to <2 months after Dose 2	0 (0.146)	17 (0.142)	100.0 (76.4, 100.0)
≥2 months to <4 months after Dose 2	0 (0.155)	10 (0.148)	100.0 (57.4, 100.0)
≥4 months after Dose 2	0 (0.061)	3 (0.055)	100.0 (-117.8, 100.0)
Dose 1 All-Available Efficacy Population	N=1131	N=1129	-
After Dose 1	3 (0.450)	48 (0.434)	94.0 (81.3, 98.8)
Dose 1 to before Dose 2	3 (0.065)	12 (0.065)	75.1 (7.6, 95.5)
Dose 2 to <7 days after Dose 2	0 (0.021)	5 (0.021)	100.0 (-8.7, 100.0)
≥7 days after Dose 2	0 (0.364)	31 (0.348)	100.0 (87.9, 100.0)

N=number of participants in the population; n=number of participants meeting the primary endpoint definition; py=person-years of surveillance.
Source: Tables 12, 13, and 15 of Interim Clinical Study Report.

Figure 1 Cumulative Incidence of COVID-19 – Dose 1 All-Available Effic opulation



Source: Figure 1 of Interim Clinical Study Report.

6.1.11.3 Subpopulation Analyses

Table 7 presents the subgroup efficacy analysis results for the Dose 1 All-Available Efficacy Population. Overall, high efficacy was observed regardless of sex or ethnicity and among White participants. The limited number of cases observed among non-White participants precludes meaningful interpretation of efficacy within this subgroup.

Table 7. Efficacy Starting at Dose 1 by Subgroup – Dose 1 All-Available Efficacy Population

Population/Surveillance Period	BNT162b2 n (1000-py)	Placebo n (1000-py)	VE (95% CI)
Overall	3 (0.450)	48 (0.434)	94.0 (81.3, 98.8)
Sex	-	-	-
Male	3 (0.227)	26 (0.223)	88.7 (63.0, 97.8)
Female	0 (0.223)	22 (0.211)	100.0 (82.7, 100.0)
Race	-	-	-
White	2 (0.384)	45 (0.367)	95.8 (83.8, 99.5)
Black or African American	0 (0.024)	2 (0.026)	100.0 (-479.7, 100.0)
Other	1 (0.042)	1 (0.042)	1.4 (-7638.0, 98.7)
Ethnicity	-	-	-
Hispanic/Latino	1 (0.055)	11 (0.051)	91.6 (42.3, 99.8)
Non-Hispanic/Non-Latino	2 (0.394)	37 (0.382)	94.8 (79.7, 99.4)

n=number of participants meeting the primary endpoint definition.
py=person-years of surveillance.
Source: Table 14.13 of Interim Clinical Study Report.

Reviewer Comment:

- *The immunogenicity and efficacy data reported by the applicant were consistent with the Study Data Tabulation Model (SDTM) data.*

6.1.12 Safety Analyses

Solicited Local and Systemic Reactions

Table 8 shows the frequency by severity of each solicited local and systemic reaction within 7 days of each dose among adolescents. In general, incidence of any redness, swelling, injection site pain, fever, fatigue, headache, chills, vomiting, new or worsened muscle pain, and new or worsened joint pain was higher among BNT162b2 recipients than among placebo recipients after either dose.

Injection site pain, fatigue, and headache were the most frequently reported solicited adverse reactions. The incidences of solicited local reactions were slightly higher after Dose 1 than after Dose 2, while the incidences of solicited systemic reactions were generally higher after Dose 2 with the exception of vomiting and diarrhea.

Among BNT162b2 recipients, the median onset day of solicited local reactions was Day 1 (i.e. day of vaccination) to Day 2 after either dose, with a median duration of 2 days. The median onset day of solicited systemic reactions was Day 2 to Day 3 after either dose, with a median duration of 1 to 2 days.

Table 8. Frequency of Solicited Reactions Within 7 Days of each Dose

-	**BNT162b2 Dose 1 N=1127 n (%)**	**Placebo Dose 1 N=1127 n (%)**	**BNT162b2 Dose 2 N=1097 n (%)**	**Placebo Dose 2 N=1078 n (%)**
Redness	-	-	-	-
Any (>2.0 cm)	65 (5.8)	12 (1.1)	55 (5.0)	10 (0.9)
Mild	44 (3.9)	11 (1.0)	29 (2.6)	8 (0.7)
Moderate	20 (1.8)	1 (0.1)	26 (2.4)	2 (0.2)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling	-	-	-	-
Any (>2.0 cm)	78 (6.9)	11 (1.0)	54 (4.9)	6 (0.6)
Mild	55 (4.9)	9 (0.8)	36 (3.3)	4 (0.4)
Moderate	23 (2.0)	2 (0.2)	18 (1.6)	2 (0.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain at the injection site	-	-	-	-
Any	971 (86.2)	263 (23.3)	866 (78.9)	193 (17.9)
Mild	467 (41.4)	227 (20.1)	466 (42.5)	164 (15.2)
Moderate	493 (43.7)	36 (3.2)	393 (35.8)	29 (2.7)
Severe	11 (1.0)	0 (0.0)	7 (0.6)	0 (0.0)
Fever	-	-	-	-
≥38.0°C	114 (10.1)	12 (1.1)	215 (19.6)	7 (0.6)
≥38.0°C to 38.4°C	74 (6.6)	8 (0.7)	107 (9.8)	5 (0.5)
>38.4°C to 38.9°C	29 (2.6)	2 (0.2)	83 (7.6)	1 (0.1)
>38.9°C to 40.0°C	10 (0.9)	2 (0.2)	25 (2.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	-	-	-	-
Any	677 (60.1)	457 (40.6)	726 (66.2)	264 (24.5)
Mild	278 (24.7)	250 (22.2)	232 (21.1)	133 (12.3)
Moderate	384 (34.1)	199 (17.7)	468 (42.7)	127 (11.8)
Severe	15 (1.3)	8 (0.7)	26 (2.4)	4 (0.4)
Headache	-	-	-	-
Any	623 (55.3)	396 (35.1)	708 (64.5)	264 (24.5)
Mild	361 (32.0)	256 (22.7)	302 (27.5)	170 (15.8)
Moderate	251 (22.3)	131 (11.6)	384 (35.0)	93 (8.6)
Severe	11 (1.0)	9 (0.8)	22 (2.0)	1 (0.1)
Chills	-	-	-	-
Any	311 (27.6)	109 (9.7)	455 (41.5)	74 (6.9)
Mild	195 (17.3)	82 (7.3)	221 (20.1)	53 (4.9)
Moderate	111 (9.8)	25 (2.2)	214 (19.5)	21 (1.9)
Severe	5 (0.4)	2 (0.2)	20 (1.8)	0 (0.0)
Vomiting	-	-	-	-
Any	31 (2.8)	10 (0.9)	29 (2.6)	12 (1.1)
Mild	30 (2.7)	8 (0.7)	25 (2.3)	11 (1.0)
Moderate	0 (0.0)	2 (0.2)	4 (0.4)	1 (0.1)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	-	-	-	-
Any	90 (8.0)	82 (7.3)	65 (5.9)	44 (4.1)
Mild	77 (6.8)	72 (6.4)	59 (5.4)	39 (3.6)

-	BNT162b2 Dose 1 N=1127 n (%)	Placebo Dose 1 N=1127 n (%)	BNT162b2 Dose 2 N=1097 n (%)	Placebo Dose 2 N=1078 n (%)
Moderate	13 (1.2)	10 (0.9)	6 (0.5)	5 (0.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New or worsened muscle pain	-	-	-	-
Any	272 (24.1)	148 (13.1)	355 (32.4)	90 (8.3)
Mild	125 (11.1)	88 (7.8)	152 (13.9)	51 (4.7)
Moderate	145 (12.9)	60 (5.3)	197 (18.0)	37 (3.4)
Severe	2 (0.2)	0 (0.0)	6 (0.5)	2 (0.2)
New or worsened joint pain	-	-	-	-
Any	109 (9.7)	77 (6.8)	173 (15.8)	51 (4.7)
Mild	66 (5.9)	50 (4.4)	91 (8.3)	30 (2.8)
Moderate	42 (3.7)	27 (2.4)	78 (7.1)	21 (1.9)
Severe	1 (0.1)	0 (0.0)	4 (0.4)	0 (0.0)
Antipyretic use	413 (36.6)	111 (9.8)	557 (50.8)	95 (8.8)

N=number of subjects responding yes or no for any reaction within 7 days of dosing.
n=number of subjects with the specified reaction.
Source: Summarized by the reviewer based on response to March 14, 2022 information request.

Unsolicited Adverse Events

Tables 9 and 10 present the numbers and percentages of adolescent participants who reported any unsolicited AE, SAE, nonserious AE, or AE leading to withdrawal after Dose 1. These numbers are reported for three separate risk windows: 1) Dose 1 to 1 month post Dose 2, 2) Dose 1 to 6 months post Dose 2, unblinding, or the September 2, 2021 data cutoff, whichever was earlier, and 3) unblinding to the cutoff.

The percentages of subjects who reported any AE were similar between BNT162b2 and placebo recipients from Dose 1 to 1 month after Dose 2, while a slightly higher percentage of placebo recipients reported any AE from Dose 1 to 6 months after Dose 2. A higher percentage of BNT162b2 recipients reported any AE considered by the investigator to be related to the study intervention in both risk windows. A total of 10 (0.9%) BNT162b2 recipients and 2 (0.2%) placebo recipients reported any SAE up to 6 months post Dose 2, none of which was considered by the investigator to be related to the study intervention. No participants died as of the cutoff. The median duration of blinded follow-up after Dose 2 was approximately 4.4 months among all participants.

A total of 1,010 subjects who originally received placebo received at least 1 dose of BNT162b2 after unblinding prior to the September 2, 2021 cutoff. Among these subjects, 6 (0.6%) reported any SAE, of whom a 12 year-old female participant reported an SAE of appendicitis 3 days after the second crossover dose that was considered by the investigator to be related to vaccination. The median duration of follow-up after unblinding was approximately 4 months among all unblinded participants.

Table 9. Number of Subjects Reporting at Least 1 AE by Time Period – Safety Population

-	**BNT162b2 1 Month Post Dose 2 or Unblinding N=1131 n (%)**	**Placebo 1 Month Post Dose 2 or Unblinding N=1129 n (%)**	**BNT162b2 6 Months Post Dose 2 or Unblinding N=1131 n (%)**	**Placebo 6 Months Post Dose 2 or Unblinding N=1129 n (%)**
Any AE	74 (6.5)	77 (6.8)	95 (8.4)	113 (10.0)
Related	36 (3.2)	24 (2.1)	36 (3.2)	24 (2.1)
Severe	7 (0.6)	2 (0.2)	13 (1.1)	5 (0.4)
Life-Threatening	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)
Any SAE	4 (0.4)	1 (0.1)	10 (0.9)	2 (0.2)
Related	0	0	0	0
Severe	2 (0.2)	0	7 (0.6)	1 (0.1)
Life-Threatening	0	1 (0.1)	1 (0.1)	1 (0.1)
Any nonserious AE	72 (6.4)	76 (6.7)	89 (7.9)	111 (9.8)
Related	36 (3.2)	24 (2.1)	36 (3.2)	24 (2.1)
Severe	5 (0.4)	2 (0.2)	6 (0.5)	4 (0.4)
Life-Threatening	1 (0.1)	0	1 (0.1)	0
Any AE leading to withdrawal	1 (0.1)	0	1 (0.1)	0

N=number of subjects who received at least 1 dose of the study intervention.
n=number of subjects reporting at least 1 event.
Source: Adapted from Table P of 508 Tables and Table 18 of Interim Clinical Study Report.

Table 10. Number of Subjects Reporting at Least 1 AE After Unblinding – Safety Population

-	**BNT162b2 Unblinding to Cutoff N=1107 n (%)**	**Placebo – BNT162b2 Crossover to Cutoff N=1010 n (%)**
Any AE	18 (1.6)	265 (26.2)
Related	4 (0.4)	242 (24.0)
Severe	3 (0.3)	12 (1.2)
Life-Threatening	0	0
Any SAE	4 (0.4)	6 (0.6)
Related	0	1 (0.1)
Severe	1 (0.1)	3 (0.3)
Life-Threatening	0	0
Any nonserious AE	14 (1.3)	262 (25.9)
Related	4 (0.4)	241 (23.9)
Severe	2 (0.2)	9 (0.9)
Life-Threatening	0	0
Any AE leading to withdrawal	0	0

N=number of subjects who received at least 1 dose of the study intervention.
n=number of subjects reporting at least 1 event.
Source: Tables 25 and 35 of Interim Clinical Study Report.

Reviewer Comments:

- *The solicited and unsolicited AEs reported in the interim clinical study report were consistent with the SDTM data.*

Myocarditis and Pericarditis

No myocarditis or pericarditis was reported during blinded follow-up. One SAE of myocarditis was identified in a 15-year-old male participant 2 days after receiving the second crossover vaccination dose of BNT162b2.

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated analysis of efficacy was performed.

8. INTEGRATED OVERVIEW OF SAFETY

No integrated analysis of safety was performed.

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

No major statistical issues affecting study conclusions were identified for the immunogenicity, efficacy and safety data. The prespecified immunobridging success criterion comparing 12 to 15 year-old neutralizing GMTs to 16 to 25 year-old GMTs from Study C4591001 was met (GMR=1.77; 95% CI: 1.50 to 2.09). High efficacy against protocol-defined COVID-19 was observed among participants in the Evaluable Efficacy Population without evidence of prior SARS-CoV-2 infection starting at 7 days post Dose 2 (VE=100%; 95% CI: 86.8% to 100%) and among participants in the Dose 1 All-Available Efficacy Population starting after Dose 1 (VE=94.0%; 95% CI: 81.3% to 98.8%). The lack of observed severe COVID-19 precludes assessment of efficacy against severe disease in this population.

The frequency and severity of local and systemic reactions were generally higher among BNT162b2 recipients than among placebo recipients after either dose. The most commonly reported adverse reactions were injection site pain, fatigue, and headache. There was no notable difference in the frequencies of any unsolicited AE between arms during blinded follow-up, while a higher percentage of BNT162b2 recipients reported any SAE (0.9%) compared to placebo recipients (0.2%). Of note, no SAE reported during blinded follow-up was considered by the investigator to be related to the study intervention. No participants died as of the cutoff. One SAE of myocarditis was reported in a 15-year-old male participant 2 days after receiving the second crossover vaccination dose of BNT162b2. One SAE of appendicitis in a 12-year-old female participant was reported 3 days after the second crossover dose and was considered by the investigator to be related to the study vaccination.

10.2 Conclusions and Recommendations

Overall, the clinical data support the effectiveness of BNT162b2. While there is some reactogenicity associated with BNT162b2, the majority of solicited adverse reactions were mild or moderate in severity and of short duration. I defer to the clinical reviewer, Dr. Susan Wollersheim, on the overall safety conclusion for BNT162b2.