Application Type	BLA, Original Application
STN	125742/0
CBER Received Date	May 18, 2021
PDUFA Goal Date	January 16, 2022
Division / Office	DVRPA /OVRR
Committee Chair	Ramachandra Naik
Clinical Reviewer(s)	Ann Schwartz; Susan Wollersheim
Project Manager	Mike Smith; Laura Gottschalk
Priority Review	Yes
Reviewer Name(s)	Lei Huang
Review Completion Date / Stamped Date	
Supervisory Concurrence	Tsai-Lien Lin, Branch Chief, VEB, DB, OBE
	John A. Scott, Director, DB, OBE
Applicant	BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)
Established Name	COVID-19 Vaccine, mRNA
(Proposed) Trade Name	COMIRNATY
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	After preparation, each 0.3 mL dose contains 30ug modified mRNA encoding SARS-CoV-2 spike glycoprotein
Dosage Form(s) and Route(s) of Administration	Injectable Suspension, Intramuscular
Dosing Regimen	Two 0.3 mL doses, 3 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 16 years of age and older.

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GLOSSARY

BIMO	Bioresearch Monitoring
BNT162b2	PfizerBioNTech COVID-19 Vaccine
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COVID-19	coronavirus disease 2019
EUA	Emergency Use Authorization
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
IR	Information request
LNP	lipid nanoparticle
modRNA	nucleoside-modified messenger RNA
NAAT	nucleic acid amplification-based test
PY	person-years
RT-PCR	reverse transcription-polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Pfizer submitted a Biologics License Application (BLA 125742/0) on May 18, 2021 to seek licensure of the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) 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 and older. The BLA is supported by safety, efficacy, and immunogenicity data from two ongoing studies (C4591001 and BNT-162-01). This statistical review focuses on the analyses of efficacy data collected during the blinded, placebo-controlled follow-up in the Phase 2/3 portion of Study C4591001.

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. In the Phase 2/3 portion of the study, 44,165 subjects aged 16 and above were randomized 1:1 to receive two doses of BNT162b2 or placebo 21 days apart. Randomization was stratified by age group. Starting December 14, 2020, following issuance of an Emergency Use Authorization (EUA), participants 16 years of age and older were systematically unblinded when eligible per local recommendations and offered BNT162b2 vaccination if they had been randomized to placebo.

In the updated efficacy analysis for cases accrued during blinded placebo-controlled follow-up (cutoff date: March 13, 2021) of Study C4591001 in participants 16 years of age and older, the estimated vaccine efficacy (VE) against confirmed COVID-19

occurring at least 7 days after Dose 2 was 91.1% (95% CI: 88.8%, 93.1%), with 77 COVID-19 cases in the BNT162b2 group compared to 833 cases in the placebo group among participants without evidence of SARS-CoV-2 infection before and during the vaccination regimen; the estimated vaccine efficacy (VE) against confirmed COVID-19 occurring at least 7 days after Dose 2 was 90.9% (95% CI: 88.5%, 92.8%), with 81 COVID-19 cases in the BNT162b2 group compared to 854 cases in the placebo group among participants with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen.

With respect to efficacy against severe COVID-19 cases occurring at least 7 days after Dose 2, the estimated VE was 95.3% (95% CI: 71.0%, 99.9%), with 1 and 21 cases in the BNT162b2 and placebo groups, respectively, among participants without evidence of SARS-CoV-2 infection; the VE result was the same among participants with or without evidence of SARS-CoV-2 infection.

Overall, the updated efficacy analysis results show that BNT162b2 provided high VE in preventing symptomatic COVID-19 and severe COVID-19 cases.

2. CLINICAL AND REGULATORY BACKGROUND

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by SARS-CoV-2, a novel coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause. On January 31, 2020, the United States Secretary of Health and Human Services (HHS) made the declaration that COVID-19 constitutes a nationwide public health emergency. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic.

The BNT162b2 vaccine, developed by BioNTech Manufacturing GmbH in partnership with Pfizer, Inc., was granted Fast Track Designation on July 7, 2020 for individuals ≥18 years of age. An Emergency Use Authorization (EUA) was granted in the U.S. on December 11, 2020 for individuals ≥16 years of age (EUA 27034). An amendment to the EUA was submitted on May 10, 2021 to support emergency use in participants 12 to 15 years of age.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to Haecin Chun's Bioresearch Monitoring (BIMO) review memo.

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

Please refer to other review disciplines' memos.

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

5.1 Review Strategy

This memo focuses on the statistical review of clinical efficacy data. Please refer to Dr. Ye Yang's memo for the statistical review of clinical safety data, and to Dr. Xinyu Tang's memo for the statistical review of non-clinical data.

To demonstrate efficacy of BNT162b2, the applicant provided the efficacy results from the interim analysis (cutoff date: November 4, 2020), the final analysis (cutoff date: November 14, 2020), and an updated analysis for cases accrued during blinded placebo-controlled follow-up (cutoff date: March 13, 2021) for Study C4591001. As the efficacy results from the interim and final analyses supported the issuance of an EUA and have been reviewed under EUA 27034, this statistical review primarily focuses on the updated efficacy results.

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

The following documents submitted to the BLA are reviewed:

125742/0 (submitted on 5/6/2021)

Module 2. Common Technical Document Summaries

- Clinical Overview
- Summary of Clinical Efficacy

Module 5. Clinical Study Reports

- C4591001 Statistical Analysis Plan
- C4591001 Interim 6-Month Report

125742/0.3 (submitted on 5/19/2021)

Module 1.11.3 Clinical Information Amendment

- Response to FDA 18 May 2021 IR

125742/0.17 (submitted on 7/26/2021)

Module 1.11.3 Clinical Information Amendment

- Response to CBER Clinical 22 July 2021 Info Request

125742/0.18 (submitted on 7/28/2021)

Module 1.11.3 Clinical Information Amendment

- Response to CBER 22 July 2021 Info Request

125742/0.27 (submitted on 8/2/2021)

Module 1.14.1 Draft Labeling

125742/0.28 (submitted on 8/02/2021)
Module 1.11.3 Clinical Information Amendment
- Response to CBER Clinical 22 July 2021 Information Request

125742/0.32 (submitted on 8/05/2021)
Module 1.11.3 Clinical Information Amendment
- Response 22 Jul 2021 – Follow-up #3

Module 5 Clinical Study Reports
- C4591001 – 508 Efficacy Tables

125742/0.38 (submitted on 8/09/2021)
Module 1.14.1 Draft Labeling
Module 5 Clinical Study Reports
- C4591001 – Source Vaccine Efficacy Tables

125742/0.49 (submitted on 8/16/2021)
Module 1.14.1 Draft Labeling
Module 5 Clinical Study Reports
- C4591001 – Follow Up Table (with and without evidence of infection)

5.3 Table of Studies/Clinical Trials

Data from two ongoing clinical studies were submitted to support the licensing application for BNT162b2 and are summarized in Table 1 below. The pivotal data are derived from a single study, C4591001, which is a multi-center, Phase 1/2/3, randomized, double-blinded, placebo-controlled safety, immunogenicity, and efficacy study; the second study, BNT162-01, is a Phase 1 safety and immunogenicity study evaluating various vaccine candidates and dose levels.

Table 1. Clinical Trials Supporting Licensure of the Pfizer-BioNTech COVID-19 Vaccine

Study Number/ Country	**Description**	**BNT162b2 (30 µg)* participants (N)**	**Placebo participants (N)**	**Study Status**
C4591001 Argentina, Brazil, Germany, S. Africa, Turkey, U.S.A.	Phase 1/2/3 randomized, placebo-controlled, observer-blind; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Phase 1[a]: 24 Phase 2/3[b]: 22085	Phase 1[a]: 6 Phase 2/3[b]: 22080	Ongoing
BNT162-01 Germany	Phase 1/2 randomized, open-label; to evaluate safety and immunogenicity, dose escalation	24	0	Ongoing

N= total number of randomized participants 16 years of age and older, as of March 13, 2021 Placebo: saline.
- Studies C4591001 and BNT162-01 started in April 2020 (first participant, first visit).
* Phase 1 studies included additional participants vaccinated with other dose levels and other mRNA vaccine candidates.
[a] Phase 1: enrolled individuals 18-85 years of age
[b] Phase 2/3: Phase 2: enrolled individuals ≥18 years of age (stratified as 18 to 55 years and 56 to 85 years); Phase 3: enrolled individuals ≥16 years of age (stratified as 16-55 years and >55 years of age).
Source: Summarized by reviewer based on information provided in Module 2 - Clinical Overview.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study C4591001

Title: Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals
First Subject First Visit: April 29, 2020
Data Cut-off: Mach 13, 2021

6.1.1 Objectives

The objectives and endpoints are presented below are for the Phase 2/3 portion of the study. The objectives for the Phase 1 portion are described in Section 6.1.2 (Design Overview).

Primary efficacy objectives

1. To evaluate the efficacy of BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants without evidence of SARS-CoV-2 infection before vaccination.

   Endpoint: COVID-19 disease based on laboratory-confirmed nucleic acid amplification-based test (NAAT) in participants with no serological or virological evidence (up to 7 days after Dose 2) of past SARS-CoV-2 infection.

2. To evaluate the efficacy of BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants with and without evidence of SARS-CoV-2 infection before vaccination.

   Endpoint: COVID-19 disease based on laboratory-confirmed NAAT

Secondary efficacy objectives

- To evaluate the efficacy of BNT162b2 against confirmed COVID-19 occurring from 14 days after Dose 2 in
  - participants without evidence of SARS-CoV-2 infection before vaccination (Dose 1)
  - participants with and without evidence of SARS-CoV-2 infection before vaccination (Dose 1)

  Endpoint: COVID-19 disease based on laboratory-confirmed NAAT

- To evaluate the efficacy of BNT162b2 against severe COVID-19 occurring from 7 days and from 14 days after Dose 2 in
  - participants without evidence of SARS-CoV-2 infection before vaccination
  - participants with and without evidence of SARS-CoV-2 infection before vaccination

  Endpoint: Severe COVID-19 disease

- To describe the efficacy of BNT162b2 against confirmed COVID-19 (CDC-defined symptoms) occurring from 7 days and from 14 days after Dose 2 in
  - participants without evidence of SARS-CoV-2 infection before vaccination
  - participants with and without evidence of infection before vaccination

  Endpoint: COVID-19 disease (CDC-defined symptoms) based on laboratory-confirmed NAAT

6.1.2 Design Overview

Study C4591001 is an ongoing, randomized, placebo-controlled, observer-blinded Phase 1/2/3 study being conducted in the U.S., Argentina, Brazil, Germany, South Africa and Turkey. Initially the study was designed as a Phase 1/2 study in healthy adults in the U.S. for vaccine candidate and dosage selection, as well as evaluation of immunogenicity and preliminary efficacy. The protocol was expanded to include a Phase 2/3 portion of the study to evaluate clinical disease efficacy endpoint in individuals 12 years of age and older in the U.S. and additional sites outside of the U.S. This review will focus on data collected from participants 16 years of age and older.

The Phase 1 portion of the study was designed to identify a preferred vaccine candidate(s) and vaccine dose level(s) for further development based on safety, tolerability, and immunogenicity. To this end, two age groups were evaluated in separate

cohorts: younger adults 18 through 55 years of age (N=45) and older adults 65 through 85 years of age (N=45). The study population included healthy men and women and excluded participants at high risk of SARS-CoV-2 infection or with serological evidence of prior or current SARS-CoV-2 infection. Two different vaccine candidates were evaluated, and younger participants received escalating dose levels Evaluation of escalating dose levels in the older age group (65 through 85 years), were based on recommendations from an internal review committee that reviewed safety and immunogenicity data. For each vaccine candidate and dose level, participants were randomized 4:1, such that 12 participants received the vaccine candidate and 3 participants received placebo. Review of the safety and immunogenicity from Phase 1, in combination with data from Study BNT162-01 (see Section 6.2 of this review), supported the final vaccine candidate and dose level (BNT162b2 at 30 μg, given 21 days apart) to proceed into Phase 2/3.

In Phase 2/3, participants were initially enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age) and a goal of 40% enrollment in the older adult age group. Adolescents 16-17 years of age (and subsequently 12-15 years of age) were added to the protocol later, based on review of safety data in younger adults enrolled in the ongoing study. The study population for Phase 2/3 includes participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19 disease, such as participants working in the healthcare field, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. Participants were randomized 1:1 to receive 2 doses of either BNT162b2 or placebo, 21 days apart. The Phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 participants enrolled early, and these participants also contribute to the overall efficacy and safety data in the Phase 3 portion.

The ongoing Phase 3 portion of the study is evaluating the safety and efficacy of BNT162b2 for the prevention of COVID-19 disease occurring at least 7 days after the second dose of vaccine. Efficacy is being assessed throughout a participant's follow-up in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness, an illness visit occurs. Assessments for illness visits include a nasal (midturbinate) swab, which is tested at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (e.g., Cepheid; FDA authorized under EUA), or other sufficiently validated NAAT, to detect SARS-CoV-2. The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory. In that case, the following NAAT results are acceptable: Cepheid Xpert Xpress SARS-CoV-2, Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001), and Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

The study design included a planned interim analysis of the first primary efficacy endpoint at pre-specified numbers of COVID-19 cases (at least 62, 92, and 120 cases), and all primary and secondary efficacy endpoints were analyzed in the final efficacy analysis after at least 164 COVID-19 cases were accrued (see Statistical Analysis section,

below). Participants are expected to participate for a maximum of approximately 26 months.

Starting December 14, 2020, following issuance of the Emergency Use Authorization for the Pfizer-BioNTech COVID-19 Vaccine, study participants 16 years of age and older have been unblinded to their treatment assignment when eligible per local recommendations, and offered BNT162b2 vaccination if they had been randomized to placebo.

The study was unblinded in stages as each participant was either individually unblinded upon eligibility for vaccination outside the study or had concluded their 6-month post–Dose 2 study visit. Every participant 16 years of age and older who participated in the Phase 2/3 study was given the opportunity to receive BNT162b2 no later than the 6-month timepoint after the second study vaccination. Participants who originally received placebo but then went on to receive BNT162b2 were moved to a new visit schedule to receive both doses of BNT162b2, 3 weeks apart.

6.1.3 Population

Individuals 12 years of age and older including those with stable infections and common comorbidities.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study C4591001 (Phase 1) evaluated a 2-dose series of investigational vaccine or placebo (0.9% normal saline) administered at a 21-day interval. Subjects were randomized to receive one of three levels of investigational RNA vaccine candidates (or placebo) for active immunization against COVID-19. The investigational RNA vaccine candidates included:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD): dose levels 10 μg, 20 μg, 30 μg, 100 μg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S): dose levels 10 μg, 20 μg, 30 μg

Based upon the preliminary results, the vaccine candidate selected for further evaluation in the Phase 2/3 studies was BNT162b2 [BNT162 RNA-LNP vaccine utilizing modRNA (b) (4) mcg/0.5 mL] at a dose of 30 μg.

6.1.6 Sites and Centers

The study was conducted in a total of 153 sites: 131 in the U.S., 9 in Turkey, 6 in Germany, 4 in South Africa, 2 in Brazil, and 1 in Argentina.

6.1.7 Surveillance/Monitoring

Please refer to Drs. Susan Wollersheim and Ann Schwartz's clinical review memo.

6.1.8 Endpoints and Criteria for Study Success

Please refer to Section 6.1.1 for efficacy endpoints.

Study success criteria:
In Phase 2/3, the assessment of VE is based on posterior probability of VE_1>30% and VE_2>30%, where VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination. Only the first primary endpoint was analyzed at interim analyses. The criteria for success at an interim analysis are based on the posterior probability, i.e. Pr(VE>30%|data) at the current number of cases. Efficacy will be declared if the posterior probability is higher than the success threshold, where the success threshold for each interim analysis was calibrated to maintain a familywise type I error rate of 2.5%. If the first primary objective is met, the second primary objective will be evaluated at the final analysis.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The statistical analyses for the Phase 1 portion were descriptive.

For Phase 2/3, the evaluable efficacy population, which included all randomized participants who received all study interventions as randomized within the predefined window and had no other important protocol deviations as determined by the clinicians, was the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population, which included all randomized subjects who received either at least 1 dose of vaccine or placebo (Dose 1 all-available set) or 2 doses (Dose 2 all-available set), were also performed.

The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. Assuming a true VE of 60%, 164 COVID-19 cases would provide 90% power to conclude true VE >30%. Because the analyses are based on the number of cases rather than the number of participants, the total number of participants enrolled in Phase 2/3 would vary depending on the incidence of COVID-19 at the time of enrollment, the true underlying VE, and a potential early stop for efficacy or futility. Four interim analyses were planned to be performed after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first IA was not performed until 94 cases were accrued, followed by the final analysis with 170 cases.

VE was evaluated using a beta-binomial model and the posterior probability of VE being >30% was assessed. A minimally informative beta prior, beta (0.700102, 1), was proposed for $\theta = r(1\text{-}VE)/(1+r(1\text{-}VE))$, where r is the ratio of surveillance time in the BNT162b2 group over that in the placebo group. For participants with multiple confirmed cases, only the first case contributed to the VE calculation. The two primary efficacy endpoints were evaluated sequentially to control the familywise type I error rate at 2.5% (one-sided). For the primary endpoint analysis, missing efficacy data were not imputed; only participants with known disease status were included. A sensitivity

analysis was performed by imputing missing values with the assumption of missing at random (MAR). Secondary endpoints were evaluated similarly to the primary endpoints.

After the final efficacy analyses at 170 cases, updated efficacy analyses on primary and secondary efficacy endpoints were performed with additional data accrued. The point estimate of VE in the blinded follow-up period and associated 2-sided 95% CI were derived using the Clopper-Pearson method, adjusting for surveillance time. The posterior probability, Pr(VE>30%|data), was also provided.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Participants 18 through 55 years of age and 56 years of age and older began enrollment into Phase 2/3 from July 27, 2020 and participants 16 through 17 years of age began enrollment from September 16, 2020.

6.1.10.1.1 Demographics

The population for the updated analysis of vaccine efficacy endpoint (March 2021 data cutoff) included 42,436 participants 16 years of age and older (21,136 in the BNT162b2 group and 21,300 in the placebo group), with or without evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. Table 2 presents the specific demographic characteristics in the studied population.

The evaluable efficacy population who received BNT162b2 included 48.6% females, 81.9% White, 9.5% African American, 4.4% Asian, and <3% from other racial groups; 25.6% of participants were Hispanic/Latino. The median age was 51 years. One or more comorbidities that increase the risk of severe COVID-19 disease were present among 46% of participants. Evidence of prior SARS-CoV-2 infection was observed in 3% of participants. Geographically, <2% of participants lived in Germany, Turkey and South Africa, 6.8% lived in Brazil, 12.7% lived in Argentina, and 76.4% of participants lived in the U.S.

Table 2. Demographics and Other Baseline Characteristics, Participants 16 Years of Age and Older, With or Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy Population (Data Cutoff March 13, 2021)

Characteristic	BNT162b2 (30 µg) (N[a]=21136) n[b] (%)	Placebo (N[a]=21300) n[b] (%)	Total (N[a]=42436) n[b] (%)
Sex: Female	10280 (48.6)	10579 (49.7)	20859 (49.2)
Sex: Male	10856 (51.4)	10721 (50.3)	21577 (50.8)
Age at Vaccination: Mean years (SD)	49.8 (16.0)	49.7 (16.0)	49.7 (16.0)
Age at Vaccination: Median (years)	51.0	51.0	51.0
Age at Vaccination: Min, max (years)	(16, 89)	(16, 91)	(16, 91)
Age Group: 16 to <18 years	370 (1.8)	362 (1.7)	732 (1.7)
Age Group: 18 to 55 years	12120 (57.3)	12252 (57.5)	24372 (57.4)
Age Group: >55 years	8646 (40.9)	8686 (40.8)	17332 (40.8)
Age Group: ≥65 years	4407 (20.9)	4429 (20.8)	8836 (20.8)
Race: American Indian or Alaska Native	204 (1.0)	190 (0.9)	394 (0.9)
Race: Asian	929 (4.4)	924 (4.3)	1853 (4.4)
Race: Black or African American	2009 (9.5)	2036 (9.6)	4045 (9.5)
Race: Native Hawaiian or Other Pacific Islander	56 (0.3)	32 (0.2)	88 (0.2)
Race: White	17304 (81.9)	17487 (82.1)	34791 (82.0)
Race: Multiracial	545 (2.6)	519 (2.4)	1064 (2.5)
Race: Not reported	89 (0.4)	112 (0.5)	201 (0.5)
Ethnicity: Hispanic or Latino	5403 (25.6)	5409 (25.4)	10812 (25.5)
Ethnicity: Not Hispanic or Latino	15628 (73.9)	15778 (74.1)	31406 (74.0)
Ethnicity: Not reported	105 (0.5)	113 (0.5)	218 (0.5)
Obesity: Yes[c]	7239 (34.2)	7386 (34.7)	14625 (34.5)
Obesity: No	13897 (65.8)	13914 (65.3)	27811 (65.5)
Comorbidities: Yes[d]	9712 (46.0)	9736 (45.7)	19448 (45.8)
Comorbidities: No	11424 (54.0)	11564 (54.3)	22988 (54.2)
Baseline evidence of prior SARS-CoV-2 infection: Negative[f]	20365 (96.4)	20511 (96.3)	40876 (96.3)
Baseline evidence of prior SARS-CoV-2 infection: Positive[e]	627 (3.0)	669 (3.1)	1296 (3.1)
Baseline evidence of prior SARS-CoV-2 infection: Missing	144 (0.7)	120 (0.6)	264 (0.6)
Country: Argentina	2686 (12.7)	2710 (12.7)	5396 (12.7)
Country: Brazil	1437 (6.8)	1432 (6.7)	2869 (6.8)
Country: Germany	240 (1.1)	243 (1.1)	483 (1.1)
Country: South Africa	391 (1.8)	392 (1.8)	783 (1.8)
Country: Turkey	241 (1.1)	238 (1.1)	479 (1.1)

Characteristic	BNT162b2 (30 µg) (N[a]=21136) n[b] (%)	Placebo (N[a]=21300) n[b] (%)	Total (N[a]=42436) n[b] (%)
Country: United States of America	16141 (76.4)	16285 (76.5)	32426 (76.4)

Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
Note: The analysis was based on treatment group as randomized.
b. n = Number of subjects with the specified characteristic.
c. Subjects who had BMI ≥30 kg/m^2.
d. Number of subjects who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as subjects who had at least one Charlson comorbidity index category or BMI ≥30 kg/m^2.
e. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
f. Negative N-binding antibody result and negative NAAT result at Visit 1 and no medical history of COVID-19.
Source: Table F of C4591001-508-efficacy-tables submitted to STN 125742/0.32.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Please refer to Drs. Susan Wollersheim and Ann Schwartz's clinical review memo.

6.1.10.1.3 Subject Disposition

The disposition of all Phase 2/3 participants 16 years of age and older is presented in Table 3. During the blinded placebo-controlled follow-up period, most participants randomized received Dose 1 (99.7%) and Dose 2 (98.0%).

Table 3. Disposition of Participants 16 Years of Age and Older, Phase 2/3 Subjects, Efficacy Population (Data Cutoff March 13, 2021)

	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	22085 (100.0)	22080 (100.0)	44165 (100.0)
Dose 1 all-available efficacy population	22009 (99.7)	22008 (99.7)	44017 (99.7)
Subjects without evidence of infection before Dose 1	21172 (95.9)	21168 (95.9)	42340 (95.9)
Subjects excluded from Dose 1 all-available efficacy population	76 (0.3)	72 (0.3)	148 (0.3)
Reason for exclusion[c]			
Did not receive at least 1 vaccination	55 (0.2)	50 (0.2)	105 (0.2)
Data considered potentially unreliable due to lack of PI oversight identified as significant quality event	21 (0.1)	22 (0.1)	43 (0.1)

	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Dose 2 all-available efficacy population	21648 (98.0)	21624 (97.9)	43272 (98.0)
Subjects without evidence of infection prior to 7 days after Dose 2	20536 (93.0)	20487 (92.8)	41023 (92.9)
Subjects excluded from Dose 2 all-available efficacy population	437 (2.0)	456 (2.1)	893 (2.0)
Reason for exclusion[c]			
Did not receive 2 vaccinations	374 (1.7)	430 (1.9)	804 (1.8)
Data considered potentially unreliable due to lack of PI oversight identified as significant quality event	21 (0.1)	22 (0.1)	43 (0.1)
Unblinded prior to 7 days after Dose 2	44 (0.2)	11 (0.0)	55 (0.1)
Evaluable efficacy (7 days) population	21136 (95.7)	21300 (96.5)	42436 (96.1)
Subjects without evidence of infection prior to 7 days after Dose 2	20064 (90.8)	20197 (91.5)	40261 (91.2)
Subjects excluded from evaluable efficacy (7 days) population	949 (4.3)	780 (3.5)	1729 (3.9)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	32 (0.1)	30 (0.1)	62 (0.1)
Data considered potentially unreliable due to lack of PI oversight identified as significant quality event	21 (0.1)	22 (0.1)	43 (0.1)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	718 (3.3)	729 (3.3)	1447 (3.3)
Unblinded prior to 7 days after Dose 2	44 (0.2)	11 (0.0)	55 (0.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	240 (1.1)	58 (0.3)	298 (0.7)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
Note: The analysis was based on treatment group as randomized.
a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Subjects may have been excluded for more than 1 reason.
Source: Table D of C4591001-508-efficacy-tables submitted to STN 125742/0.32.

Reviewer Comment

1. *There were more protocol deviations leading to exclusion from analyses in the BNT162b2 group than in the placebo group. The majority of protocol deviations were in the category of investigational products, including dosing/administration error and investigational product deemed not suitable for use. Protocol deviations in other categories appeared balanced across the two treatment groups. The additional analysis on the all-available efficacy population may be regarded as a sensitivity analysis and showed very similar efficacy results.*
2. *The Dose 1 all-available efficacy population excluded 43 subjects (21 in the BNT162b2 group and 22 in the placebo group) due to a specific protocol*

deviation, i.e. data considered potentially unreliable due to lack of PI oversight identified as a significant quality event, while the Dose 1 all-available set is defined as all randomized participants who received at least 1 vaccination in the SAP. I conducted a sensitivity analysis without excluding these 43 subjects for efficacy analyses using the Dose 1 all-available population, when applicable, and it showed minimal impact on VE results.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints

The Interim and Final Analyses

At the interim analysis, there were 4 confirmed COVID-19 cases in the BNT162b2 group and 90 confirmed cases in the placebo group among subjects without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2, resulting in a VE point estimate of 95.5% (95% credible interval: 88.8%, 98.4%) and a 99.99% posterior probability for the true VE being >30%, which met the prespecified success criterion of posterior probability >99.5%. The median follow-up duration for subjects included in the first interim efficacy analysis was slightly less than the planned 2 months. In the final analysis, the case split between the BNT162b2 and placebo groups was 8:162 (VE: 95.0%; 95% credible interval: 90.3%, 97.6%) among subjects without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2, and 9:169 (VE: 94.6%; 95% credible interval: 89.9%, 97.3%) among subjects with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. The final analysis extended the median follow-up for these subjects to greater than 2 months, and the results indicate that the conclusions from the first interim efficacy analysis would not change when including additional follow-up to November 14, 2020. This pre-specified primary efficacy analysis was the basis for issuance of the Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 Vaccine on December 10, 2020.

Reviewer Comment

1. *The efficacy results presented above included 88 subjects 12-15 years of age (46 in the BNT162b2 group and 42 in the placebo group). Since none of these 12-15 years old subjects developed protocol defined cases and the number of subjects is small relative to the evaluable population, the efficacy results excluding these subjects are very similar to the results including them. Based on my calculation, VE for 16 years and older subjects is 94.6% (95% credible interval: 90.3%, 97.6%).*
2. *The interim and final analyses were reviewed under EUA 27034, and hence the review is not replicated for this BLA submission.*

Updated Efficacy Analyses

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through March 13, 2021,

representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, the updated VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 91.1%. The case split was 77 COVID-19 cases in the BNT162b2 group compared to 833 COVID-19 cases in the placebo group (Table 4).

Table 4. Updated Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection – Evaluable Efficacy Population, 16 Years and Older (Data Cutoff March 13, 2021)

Pre-specified Age Group	BNT162b2 (N[a]=19993) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a]=20118) Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
All participants	77 6.092 (19711)	833 5.857 (19741)	91.1 (88.8, 93.1)
16 to 55 years	52 3.593 (11517)	568 3.439 (11533)	91.2 (88.3, 93.5)
>55 years and older	25 2.499 (8194)	265 2.417 (8208)	90.9 (86.2, 94.2)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
Source: Table H of C4591001-508-efficacy-tables submitted to STN 125742/0.32.

Reviewer Comment

1. *One subject (C4591001 (b) (6)) reported "covid-19 antibody test positive" in medical history but was included in the VE analysis in participants without evidence of prior infection in Table 4. An information request (IR) was sent on July 22, 2021. In the IR response submitted on July 26, 2021, the applicant clarified that "without evidence of prior infection" was based only on the NAAT tests at Visits 1 and 2 and the N-binding assay results due to the*

potential uncertainty of a medical history entry without knowledge of circumstances, assay performed, etc. Because this subject received placebo and was not a case, inclusion of subject would result in no real change to the VE estimate.

2. *A total of 9 participants in the placebo group with COVID-19 symptoms starting on the same day of unblinding with PCR confirmation either on the same day or a few days after, were included in these analyses as positive cases.*
3. *Initially, there was one additional case reported in the placebo group, for Subject C4591001* (b) (6) *. This subject reported three COVID symptom episodes: from October 8, 2020 to October 16, 2020, November 2, 2020 to December 11, 2020, and December 17, 2020 to January 16, 2021 (referred to as Episodes A, B and C, respectively). The PCR tests were negative for the first two episodes and positive for Episode C. Since the three episodes were more than 4 days apart, they should be treated as separate episodes per the statistical analysis plan (SAP). Hence, this subject should be considered to be a case with an onset on December 17, 2020, one day after the unblinding on December 16, 2020, and should be excluded from the analysis. In the IR response submitted on July 26, 2021, the applicant explained that Episodes B and C were merged into one episode as this subject was hospitalized from* (b) (6) *to* (b) (6) *, connecting Episodes B and C. We did not agree with the merging of the two episodes, because hospitalization is not a symptom or criterion pre-specified in the protocol for COVID-19 definition and there were no other data that could corroborate that this hospitalization was due to COVID-19. The applicant agreed to remove this case and updated efficacy tables were submitted on August 5, 2021.*
4. *The set of subjects used for efficacy analyses excluded those who had reported COVID symptoms but had missing or unknown PCR results at any time. It may be reasonable to exclude subjects who had reported COVID symptoms but had missing/unknown PCR results prior to 7 days after Dose 2 for efficacy analyses in participants without evidence of prior infection. However, subjects who reported symptoms and had missing/unknown PCR results after 7 days post Dose 2 were also excluded from the risk set, while they were at risk for the efficacy endpoint (lab-confirmed COVID-19 starting from 7 days post Dose 2). An IR was sent to the applicant on July 22, 2021. In the IR response submitted on July 26, 2021, the applicant explained that subjects who reported symptoms and had missing/unknown PCR results do not have a chance to be counted in the numerator and inclusion of these subjects may result in an underestimation of the incidence rate. Since the percentages of such subjects were small and slightly higher in the placebo group, excluding them from the analyses likely had minimal impact on VE results. Per our request, the applicant also provided a sensitivity analysis under the missing at random (MAR) assumption, where missing efficacy endpoints were imputed based on predicted probability from logistic regression model using the fully conditional specification method for a total of 648 subjects (279 in BNT162b2 group and 369 in placebo group) in the evaluable population who reported COVID-19 symptoms from 7 days post Dose 2 but had missing/unknown PCR results. As a supplementary sensitivity analysis, the*

applicant also applied a conservative approach to the model by assuming a higher than the observed case rate when imputing missing efficacy endpoints from participants in the BNT162b2 group only, to reflect potentially unknowable missing not at random effects that are unfavorable for efficacy result of the study. As shown in Table 5, the average VE after imputation was 90.76% under the MAR assumption, which is consistent with the efficacy results reported in Table 4. The sensitivity analyses under the missing-not-at-random assumptions show that the efficacy results are robust, e.g. at least a 16-fold increase of positivity rate in the BNT162b2 group is required for the average VE to fall below 70%, which we do not consider to be a plausible scenario.

Table 5. Sensitivity and Robustness Analysis of Missing Laboratory Results for Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Assumed Missing Data Mechanism	Average Positive Rate (%) Across all Imputations (BNT162b2: Placebo)[a]	Infection Rates Based on Existing and Imputed Values (BNT162b2: Placebo)[b]	Median Posterior Probability of VE>30%	Median of Lower Limit of 95% CI for VE	Median VE (%)	Average VE (%)
MAR	4.0:28.5	4.21:45.31	100.00	88.56	90.78	90.76
MNAR1	10.1:28.5	5.01:45.31	100.00	86.55	88.97	88.98
MNAR2	23.3:28.5	6.76:45.31	100.00	82.30	85.12	85.14
MNAR3	45.3:28.5	9.69:45.31	100.00	75.36	78.79	78.69
MNAR4	69.1:28.5	12.85:45.31	100.00	67.71	71.78	71.75
MNAR5	85.9:28.5	15.08:45.31	100.00	62.36	66.81	66.85

Abbreviations: MAR = missing at random; MNAR = missing not at random; VE = vaccine efficacy.
Note: Each row of this table represents summary results from 500 imputations that were generated using SAS PROC MI Fully Conditional Specification (FCS) method. Each imputation filled in the missing laboratory results based on a logistic regression model at the subject level, under the assumed missing data mechanism.
a. Average positive rate for each vaccine group was calculated as the mean of positive rates across all imputations among subjects with missing data after each imputation. Under the MAR assumption, the imputation model assumes the probability of positive cases for each vaccine group to be the same as observed from subjects with no missing data in that group. Under each MNAR assumption, while keeping the imputation model for placebo group unchanged, an increase in the positive rate for the BTN162b2 group was assumed to reflect a potential conservative and unknowable MNAR scenario for efficacy results of the study.
b. Infection rate in each vaccine group was the number of cases divided by a total number of subjects in that vaccine group times 1000.
Source: Adapted from Table 1 of response-22jul2021-followup submitted to STN 125742/0.28.

For participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, the updated VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 90.9%, with 81 and 854 cases in the BNT162b2 and placebo groups, respectively (Table 6).

Table 6. Updated Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants With or Without Evidence of Prior SARS-CoV-2 Infection – Evaluable Efficacy Population, 16 Years and Older (Data Cutoff March 13, 2021)

Pre-specified Age Group	BNT162b2 (N[a]=21047) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a]=21210) Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
All participants	81 6.340 (20533)	854 6.110 (20595)	90.9 (88.5, 92.8)
16 to 55 years	56 3.766 (12088)	584 3.619 (12142)	90.8 (87.9, 93.1)
>55 years and older	25 2.573 (8445)	270 2.492 (8453)	91.0 (86.5, 94.3)

Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
Source: Table I of C4591001-508-efficacy-tables submitted to STN 125742/0.32.

VE in participants in the all-available efficacy population was similar to results in the evaluable efficacy population (Table 7). The VE for the prevention of COVID-19 disease after Dose 1 is 87.6%, in the all-available efficacy population. Based on the number of cases accumulated after Dose 1 and before Dose 2, there seems to be some protection against COVID-19 disease following one dose (VE=56.4%); however, these data do not provide information about longer term protection beyond 21 days after a single dose.

Table 7. Primary Efficacy Endpoint – Participants 16 Years of Age and Older – Dose 1 All-Available Efficacy Population (Data Cutoff March 13, 2021)

Efficacy Endpoint Subgroup	BNT162b2 (N[a]=21909) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a]=21908) Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence after Dose 1	128 8.155 (21385)	998 7.874 (21315)	87.6 (85.1, 89.8)
After Dose 1 to before Dose 2	43 1.273 (21385)	98 1.266 (21315)	56.4 (37.0, 70.3)
Dose 2 to 7 days after Dose 2	3 0.403 (21049)	30 0.401 (20952)	90.0 (68.0, 98.1)
≥7 Days after Dose 2	82 6.479 (21019)	870 6.207 (20901)	91.0 (88.7, 92.9)

Abbreviation: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
Source: Table O of C4591001-508-efficacy-tables submitted to STN 125742/0.32.

Reviewer Comment
As mentioned, the Dose 1 all-available efficacy population excluded 43 subjects with a protocol deviation of data being considered potentially unreliable due to lack of PI oversight identified as a significant quality event. In my additional analysis with these subjects included, the case split for the first COVID-19 occurrence after dose 1 is 129:1003, resulting in an estimated VE of 87.6% (95% CI: 85.1%, 89.7%). Hence, the exclusion of these subjects likely had minimal impact on the VE results.

6.1.11.2 Analyses of Secondary Endpoints

Protocol-Defined Severe cases

Updated efficacy analyses of the secondary efficacy endpoint for the use of BNT162b2 for the prevention of severe COVID-19 were also evaluated. Vaccine efficacy against severe COVID-19 is presented in Table 8 for participants without prior SARS-CoV-2 infection. In the updated analysis, among participants without evidence of prior infection, the estimated VE against severe COVID-19 disease occurring at least 7 days after Dose 2 was 95.3% (71.0%, 99.9%), with one subject who received BNT162b2 and 21

participants who received placebo experiencing severe disease. The same number of severe cases were reported among participants with or without evidence of prior infection and the estimated VE was the same (95.3%). These updated analyses of the secondary vaccine efficacy with a larger number of severe cases now shows more definitive evidence of protection against severe COVID-19 disease offered by BNT162b2 (the data from the November 14, 2020 cut-off were limited to 4 total severe cases).

Table 8. First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Participants 16 Years of Age and Older – Evaluable Efficacy Population (Data Cutoff March 13, 2021)

Secondary Efficacy Endpoint	**BNT162b2 (N[a]=19993) Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo (N[a]=20118) Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)[e]**
First severe COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection	1 6.103 (19711)	21 5.971 (19741)	95.3 (71.0, 99.9)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
Source: Table M of C4591001-508-efficacy-tables submitted to STN 125742/0.32.

In the all-available efficacy population, 31 participants had severe COVID-19 disease after Dose 1 (one subject who received BNT162b2 and 30 participants who received placebo) as summarized in Table 9.

Table 9. First Severe COVID-19 Occurrence After Dose 1 – Participants 16 Years of Age and Older – Dose 1 All-Available Efficacy Population (Data Cutoff March 13, 2021)

Secondary Efficacy Endpoint	BNT162b2 (N[a]=21909) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a]=21908) Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First severe case occurrence after Dose 1	1 8.181 (21385)	30 8.032 (21316)	96.7 (80.3, 99.9)
After Dose 1 to before Dose 2	0 1.285 (21385)	6 1.293 (21316)	100.0 (14.6, 100.0)
Dose 2 to 7 days after Dose 2	0 0.403 (21056)	1 0.402 (20962)	100.0 NA
≥7 Days after Dose 2	1 6.493 (21029)	23 6.337 (20940)	95.8 (73.9, 99.9)

Abbreviation: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
Source: Table N of C4591001-508-efficacy-tables submitted to STN 125742/0.32.

Severe Case Based on CDC-Definition

Vaccine efficacy against severe COVID-19 based on the CDC definition is presented for participants with or without prior SARS-CoV-2 infection (Table 10) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARSCoV2 infection in both the vaccine and placebo groups.

Table 10. First Severe COVID-19 Occurrence Based on CDC-Definition From 7 Days After Dose 2 – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Participants 16 Years of Age and Older – Evaluable Efficacy Population (Data Cutoff March 13, 2021)

Efficacy Endpoint	BNT162b2 (N[a]=21047) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a]=21210) Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First severe COVID-19 occurrence based on CDC-definition from 7 days after Dose 2	0 6.345 (20513)	31 6.225 (20593)	100.0 (87.6, 100.0)

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
Source: Adapted from Table ADC19EF_VE_SEV_7PD2_CDC_EVAL of C4591001-ve-tables submitted to STN 125742/0.38.

6.1.11.3 Subpopulation Analyses

VE point estimates for the primary endpoint in participants without evidence of prior infection were comparable across sex, age groups (16 to 55 years and >55 years), race, ethnicity, and country, excluding categories with too few cases to analyze. Additional subgroup analyses were performed for the second vaccine efficacy endpoint (i.e. COVID-19 for participants with and without evidence of infection prior to vaccination) because this endpoint may generalize better to the population who may receive the vaccine, as baseline evidence of prior infection may not be known by all people who might receive the vaccine. VE point estimates were generally high (>84%) across the subgroups examined (i.e. sex, age, race, ethnicity, comorbidity, baseline SARS-CoV-2 status, and country) with the exception of participants identified as positive or unknown for baseline SARS-CoV-2 status and with un-reported ethnicity, for which there were too few COVID-19 cases to interpret efficacy data for these subgroups.

6.1.11.4 Dropouts and/or Discontinuations

Dropouts and discontinuations are generally balanced across the groups. There were 352 (1.6%) participants in the BNT162b2 group and 528 (2.4%) participants in the placebo group who discontinued from the vaccination period (Dose 1 to 1 month after Dose 2). Most participants completed the visit at 1 month post-Dose 2 (≥96.4%). Few participants in the BNT162b2 and placebo groups were withdrawn from the study (1.6% and 2.2%,

respectively), and most were due to withdrawals by the participant, or they were lost to follow-up without other cause given.

Starting December 14, 2020, following issuance of the Emergency Use Authorization for the Pfizer-BioNTech COVID-19 Vaccine, study participants 16 years of age and older have been unblinded to their treatment assignment when eligible per local recommendations, and offered BNT162b2 vaccination if they had been randomized to placebo. The length of blinded follow-up appears to be balanced between the BNT162b2 and placebo groups. During the blinded placebo-controlled follow-up period, 52.4% of participants in the BNT162b2 group and 52.6% of participants in the placebo group in the evaluable efficacy population with or without evidence of infection prior to 7 days after dose 2 had follow-up time between ≥4 months to <6 months after Dose 2, and 8.4% in the BNT162b2 group and 6.1% in the placebo group had follow up ≥6 months.

6.1.11.5 Exploratory and Post Hoc Analyses

Not Applicable.

6.1.12 Safety Analyses

Please refer to Dr. Ye Yang's memo for the statistical review of the clinical safety data of Study C4591001.

7. INTEGRATED OVERVIEW OF EFFICACY

Data supporting the effectiveness of the vaccine were primarily generated in Study C4591001. Consequently, no pooled efficacy analyses were performed.

8. INTEGRATED OVERVIEW OF SAFETY

Please refer to Dr. Ye Yang's memo for the statistical review of the clinical safety data.

9. ADDITIONAL STATISTICAL ISSUES

Not Applicable.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

In the updated efficacy analysis for cases accrued during blinded placebo-controlled follow-up (cutoff date: March 13, 2021) of Study C4591001 in participants 16 years of age and older, the estimated vaccine efficacy (VE) against confirmed COVID-19 occurring at least 7 days after Dose 2 was 91.1% (95% CI: 88.8%, 93.1%), with 77 COVID-19 cases in the BNT162b2 group compared to 833 cases in the placebo group among participants without evidence of SARS-CoV-2 infection before and during the vaccination regimen; the estimated vaccine efficacy (VE) against confirmed COVID-19 occurring at least 7 days after Dose 2 was 90.9% (95% CI: 88.5%, 92.8%), with 81 COVID-19 cases in the BNT162b2 group compared to 854 cases in the placebo group

among participants with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen.

With respect to efficacy against severe COVID-19 cases occurring at least 7 days after Dose 2, the estimated VE was 95.3% (95% CI: 71.0%, 99.9%), with 1 and 21 cases in the BNT162b2 and placebo groups, respectively, among participants without evidence of SARS-CoV-2 infection; the VE result was the same among participants with or without evidence of SARS-CoV-2 infection.

10.2 Conclusions and Recommendations

Overall, the updated efficacy analysis results show that BNT162b2 provided high VE in preventing symptomatic COVID-19 and severe COVID-19 cases that is consistent with the VE results reported in the interim and final analyses.