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	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
Supervisory Concurrence	John Scott, Director, DB
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 16 years of age and older

Table of Contents

GLOSSARY

ADaM	Analysis Data Model
AE	Adverse Event
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
COVID-19	Coronavirus Disease 2019
EUA	Emergency Use Authorization
HIV	Human Immunodeficiency Virus
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

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 safety data from subjects aged 16 years and above in the Phase 2/3 part of Study C4591001 collected up to the March 13, 2021 data cut-off.

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 (younger adults 18 through 55 years of age and older adults >55 years of age; adolescents 16 to 17 were later added via a protocol amendment) with 40.6% of the final study population being older adults. Since December 14, 2020, following issuance of the 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.

For all 44,047 randomized participants who received at least one dose of the study intervention, unsolicited adverse events (AEs) and serious AEs (SAEs) were collected from Dose 1 up to the March 13, 2021 data cut-off. A reactogenicity subset of approximately 4,900 participants per arm who received at least one dose of the study intervention recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose.

No major statistical issues were identified for the safety data during review. A higher percentage of subjects in the BNT162b2 group reported solicited local and systemic reactions than placebo recipients in both the younger (16 to 55 years) and older (>55 years) adult age groups after both doses. There was an imbalance in the frequencies of unsolicited AEs in the vaccine group, driven largely by increased reactogenicity. In addition, one report of pericarditis was identified in a 66-year-old male participant 28 days after receiving Dose 2 of BNT162b2. There were no reports of myocarditis in the vaccine arm up to the data cut-off. There were no major imbalances in reported SAEs, AEs leading to withdrawal, or deaths between the treatment groups at one month and up to six months after the second dose or unblinding/data cut-off.

2. Clinical and Regulatory Background

The Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) was granted Fast Track Designation for individuals ≥18 years of age on July 7, 2020, and was authorized under an Emergency Use Authorization (EUA) on December 11, 2020 for individuals ≥16 years of age. The EUA was amended to include individuals ≥12 years of age on May 10, 2021. Pfizer submitted a BLA on May 18, 2021 to seek licensure of the vaccine for active

immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

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 Haecin Chun'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 safety data from subjects aged 16 years and above in the Phase 2/3 part of Study C4591001 collected up to the March 13, 2021 data cut-off.

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 Safety

Module 5. Clinical Study Reports

125742/0/1 (submitted on 5/18/2021)

Module 1. Administrative Information and Prescribing Information

125742/0/3 (submitted on 5/19/2021)

Module 1. Administrative Information and Prescribing Information

- Response to May 18, 2021 Information Request

125742/0/26 (submitted on 8/2/2021)

Module 1. Administrative Information and Prescribing Information

- Response to July 29, 2021 Information Request

125742/0/37 (submitted on 8/9/2021)

Module 5. Clinical Study Reports

- C4591001 – 508 Safety Tables

5.3 Table of Studies/Clinical Trials

Data from two ongoing clinical studies were submitted to support the BLA for BNT162b2 and are summarized in Table 1 below. Study C4591001 is a multi-center, Phase 1/2/3, randomized, double-blinded, placebo-controlled safety, immunogenicity, and efficacy study and 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: 24 (U.S.A.) Phase 2/3: 22085 Argentina: 2887 Brazil:1452 Germany: 250 South Africa: 401 Turkey: 251 U.S.A.: 16844	Phase 1: 6 (U.S.A.) Phase 2/3: 22080 Argentina: 2889 Brazil:1448 Germany: 250 South Africa: 399 Turkey: 249 U.S.A.: 16845	Ongoing
BNT162-01 Germany	Phase 1/2 randomized, open-label; to evaluate safety and immunogenicity,	Phase 1: 24 (Germany)	0	Ongoing

Source: Summarized by the reviewer based on information provided in Module 2. Clinical Overview.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study C4591001

Title of Study: A 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

Primary Safety Objective (Phase 2/3):

- To characterize the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3

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. In the Phase 2/3 portion of the study, 43,998 subjects were planned

to be randomized 1:1 to receive two doses of BNT162b2 or placebo 21 days apart. Randomization was stratified by age group (younger adults 18 through 55 years of age, older adults >55 years of age) with a goal of 40% enrollment among older adults. Eligibility was later expanded to include adolescents 16 to 17 years of age.

Efficacy was assessed throughout the study via surveillance for potential cases of COVID-19. Participants who developed acute respiratory illness were tested for SARS-CoV-2 infection using reverse transcription-polymerase chain reaction (RT-PCR) in an illness visit. The study included planned interim analyses of the primary efficacy endpoint at 62, 92, and 120 cases, and a final analysis of all primary and secondary efficacy endpoints after at least 164 COVID-19 cases were accrued. Participants were to be followed for a maximum of 26 months. Efficacy assessments and results are covered in detail in Dr. Lei Huang's statistical review memo.

Since December 14, 2020 following issuance of the EUA, participants 16 years of age and older were systematically unblinded and, when eligible per local recommendations, offered BNT162b2 vaccination no later than the 6-month timepoint after the second study vaccination if they had been randomized to placebo.

A subset of at least 6,000 participants (the reactogenicity subset, planned to be the first 6,000 or more patients randomized) were to record local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. For all participants, unsolicited adverse events (AEs) and serious AEs (SAEs) were collected from Dose 1 up to the March 13, 2021 data cut-off.

6.1.3 Population

The Phase 2/3 study population consisted of participants 12 years of age and older at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

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 153 sites across the United States (131), Turkey (9), Germany (6), South Africa, (4), Brazil (2) and Argentina (1) participated in the study.

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

The safety endpoints for all subjects include the occurrence of AEs and SAEs from Dose 1 up to one month post Dose 2 or unblinding (whichever is earlier), and from Dose 1 up to six months post Dose 2 or unblinding. For the reactogenicity subset, safety endpoints additionally include the occurrence of local reactions (redness, swelling, and injection

site pain) and systemic reactions (fever, fatigue, headache, chills, vomiting, diarrhea, and muscle and joint pain) within seven days of each dose.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Solicited safety analyses were based on subjects in the reactogenicity subset who received at least one dose of the study intervention and responded yes or no to any reaction within seven days of each dose. Unsolicited safety analyses were based the Safety Population, which consisted of all subjects randomized in the Phase 2/3 study who received at least one dose of study intervention, analyzed according to the intervention received. Safety endpoints were summarized descriptively by computing the number and percentage of participants within the analysis set who reported at least one event.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 2 shows the disposition of randomized subjects ≥16 years of age in the Phase 2/3 portion of the study. A total of 44,165 subjects were randomized. The percentages of subjects who received each dose were similar between the vaccine and placebo groups. More subjects withdrew from the study in the placebo group than in the vaccine group.

Table 2. Subject Disposition

-	**BNT162b2 N=22085 n (%)**	**Placebo N=22080 n (%)**	**Total N=44165 n (%)**
Randomized	22085 (100.0)	22080 (100.0)	44165 (100.0)
Not vaccinated	55 (0.2)	50 (0.2)	105 (0.2)
Vaccinated	22030 (99.8)	22030 (99.8)	44060 (99.8)
Dose 1	22030 (99.8)	22030 (99.8)	44060 (99.8)
Dose 2	21675 (98.1)	21650 (98.1)	43325 (98.1)
Withdrawn from the study	343 (1.6)	484 (2.2)	827 (1.9)
Lost to follow-up	174 (0.8)	191 (0.9)	365 (0.8)
Withdrawal by subject	122 (0.6)	226 (1.0)	348 (0.8)
Protocol deviation	11 (<0.1)	24 (0.1)	35 (0.1)
Death	16 (0.1)	15 (0.1)	31 (0.1)
Adverse event	9 (<0.1)	8 (<0.1)	17 (<0.1)
Physician decision	3 (<0.1)	6 (<0.1)	9 (<0.1)
No longer meets eligibility criteria	1 (<0.1)	4 (<0.1)	5 (<0.1)
Pregnancy	0	1 (<0.1)	1 (<0.1)
Medication error without AE	1 (<0.1)	0	1 (<0.1)
Withdrawal by parent/guardian	1 (<0.1)	0	1 (<0.1)
Other	5 (<0.1)	9 (<0.1)	14 (<0.1)

Source: Adapted from Table 31 of Summary of Clinical Safety.

6.1.10.1.1 Demographics

Table 3 presents demographic characteristics for the Safety Population. Demographic characteristics were generally similar with regard to age, gender, race, and ethnicity

among participants who received BNT162b2 and those who received placebo. Overall, among all the participants who received either BNT162b2 or placebo, 50.9% were male and 49.1% were female, 82.0% were White, 9.6% were Black or African American, 4.3% were Asian, and 1.0% were American Indian or Alaska Native.

Table 3. Demographics Characteristics of the Safety Population

-	**BNT162b2 N=22026 n (%)**	**Placebo N=22021 n (%)**	**Total N=44047 n (%)**
Sex			
Male	11322 (51.4)	11098 (50.4)	22420 (50.9)
Female	10704 (48.6)	10923 (49.6)	21627 (49.1)
Race			
White	18056 (82.0)	18064 (82.0)	36120 (82.0)
Black/African-American	2098 (9.5)	2118 (9.6)	4216 (9.6)
American Indian/Alaskan Native	221 (1.0)	217 (1.0)	438 (1.0)
Asian	952 (4.3)	942 (4.3)	1894 (4.3)
Native Hawaiian/Other Pacific Islander	58 (0.3)	32 (0.1)	90 (0.2)
Multiracial	550 (2.5)	533 (2.4)	1083 (2.5)
Not Reported	91 (0.4)	115 (0.5)	206 (0.5)
Ethnicity			
Hispanic/Latino	5704 (25.9)	5695 (25.9)	11399 (25.9)
Non-Hispanic/Non-Latino	16211 (73.6)	16212 (73.6)	32423 (73.6)
Not Reported	111 (0.5)	114 (0.5)	225 (0.5)
Country			
Argentina	2883 (13.1)	2881 (13.1)	5764 (13.1)
Brazil	1452 (6.6)	1448 (6.6)	2900 (6.6)
Germany	249 (1.1)	250 (1.1)	499 (1.1)
South Africa	401 (1.8)	399 (1.8)	800 (1.8)
Turkey	249 (1.1)	249 (1.1)	498 (1.1)
USA	16792 (76.2)	16794 (76.3)	33586 (76.3)
Age Group			
16-55 Years	13069 (59.3)	13095 (59.5)	26164 (59.4)
>55 Years	8957 (40.7)	8926 (40.5)	17883 (40.6)
Age			
Mean (Standard Deviation)	49.7 (16.0)	49.6 (16.1)	49.7 (16.0)
Median	51.0	51.0	51.0
Minimum, Maximum	(16, 89)	(16, 91)	(16, 91)

Source: Table 4 of Summary of Clinical Safety.

6.1.11 Efficacy Analyses

Please refer to Dr. Lei Huang's statistical review memo.

6.1.12 Safety Analyses

Solicited Local and Systemic Reactions

Tables 4 and 5 present the frequency by severity of each solicited local and systemic reaction within seven days of each dose for the 16-to-55 and 56-and-above year-old age

groups, respectively. In general, incidence of any redness, swelling, injection site pain, fever, fatigue, headache, chills, new or worse muscle pain, and new or worse joint pain was higher among vaccine recipients than among placebo recipients. There were no notable differences between vaccine and placebo recipients or between vaccine Dose 1 and Dose 2 for vomiting or diarrhea.

For both age groups, injection site pain was the most frequent solicited local adverse reaction. After Dose 2, the younger age group reported any pain more frequently than the older age group (78.3% vs 66.1%). A similar pattern was observed after Dose 1. Frequencies of any injection site redness and swelling were generally similar after each dose and for both age groups.

Among BNT162b2 recipients 16 to 55 years of age, the mean duration (not shown in tables) of pain at the injection site after Dose 2 was 2.5 days (range 1 to 70 days), 2.2 days for redness (range 1 to 9 days), and 2.1 days for swelling (range 1 to 8 days). Among BNT162b2 recipients 56 years of age and older the mean duration of pain at the injection site after Dose 2 was 2.4 days (range 1 to 36 days), 3.0 days for redness (range 1 to 34 days), and 2.6 days for swelling (range 1 to 34 days).

The frequency and severity of systemic AEs were generally higher in the younger age group. Within each age group, the frequency and severity of systemic AEs were higher after Dose 2 than Dose 1, except for vomiting and diarrhea, which were generally similar regardless of dose. For both age groups, fatigue, headache and new/worsened muscle pain were the most common reactions after Dose 2.

Table 4. Frequency of Solicited Reactions Within Seven Days of each Dose (16 to 55 Years)

-	**BNT162b2 Dose 1 N=2899 n (%)**	**Placebo Dose 1 N=2908 n (%)**	**BNT162b2 Dose 2 N=2682 n (%)**	**Placebo Dose 2 N=2684 n (%)**
Redness	-	-	-	-
Any (>2.0 cm)	156 (5.4)	28 (1.0)	151 (5.6)	18 (0.7)
Mild	113 (3.9)	19 (0.7)	90 (3.4)	12 (0.4)
Moderate	36 (1.2)	6 (0.2)	50 (1.9)	6 (0.2)
Severe	7 (0.2)	3 (0.1)	11 (0.4)	0
Swelling	-	-	-	-
Any (>2.0 cm)	184 (6.3)	16 (0.6)	183 (6.8)	5 (0.2)
Mild	124 (4.3)	6 (0.2)	110 (4.1)	3 (0.1)
Moderate	54 (1.9)	8 (0.3)	66 (2.5)	2 (0.1)
Severe	6 (0.2)	2 (0.1)	7 (0.3)	0
Pain at the injection site	-	-	-	-
Any	2426 (83.7)	414 (14.2)	2101 (78.3)	312 (11.6)
Mild	1464 (50.5)	391 (13.4)	1274 (47.5)	284 (10.6)
Moderate	923 (31.8)	20 (0.7)	788 (29.4)	28 (1.0)
Severe	39 (1.3)	3 (0.1)	39 (1.5)	0
Fever	-	-	-	-
≥38.0°C	119 (4.1)	25 (0.9)	440 (16.4)	11 (0.4)
≥38.0°C to 38.4°C	86 (3.0)	16 (0.6)	254 (9.5)	5 (0.2)

-	**BNT162b2 Dose 1 N=2899 n (%)**	**Placebo Dose 1 N=2908 n (%)**	**BNT162b2 Dose 2 N=2682 n (%)**	**Placebo Dose 2 N=2684 n (%)**
>38.4℃ to 38.9℃	25 (0.9)	5 (0.2)	146 (5.4)	4 (0.1)
>38.9℃ to 40.0℃	8 (0.3)	4 (0.1)	39 (1.5)	2 (0.1)
>40.0℃	0	0	1 (0.0)	0
Fatigue	-	-	-	-
Any	1431 (49.4)	960 (33.0)	1649 (61.5)	614 (22.9)
Mild	760 (26.2)	570 (19.6)	558 (20.8)	317 (11.8)
Moderate	630 (21.7)	372 (12.8)	949 (35.4)	283 (10.5)
Severe	41 (1.4)	18 (0.6)	142 (5.3)	14 (0.5)
Headache	-	-	-	-
Any	1262 (43.5)	975 (33.5)	1448 (54.0)	652 (24.3)
Mild	785 (27.1)	633 (21.8)	699 (26.1)	404 (15.1)
Moderate	444 (15.3)	318 (10.9)	658 (24.5)	230 (8.6)
Severe	33 (1.1)	24 (0.8)	91 (3.4)	18 (0.7)
Chills	-	-	-	-
Any	479 (16.5)	199 (6.8)	1015 (37.8)	114 (4.2)
Mild	338 (11.7)	148 (5.1)	477 (17.8)	89 (3.3)
Moderate	126 (4.3)	49 (1.7)	469 (17.5)	23 (0.9)
Severe	15 (0.5)	2 (0.1)	69 (2.6)	2 (0.1)
Vomiting	-	-	-	-
Any	34 (1.2)	36 (1.2)	58 (2.2)	30 (1.1)
Mild	29 (1.0)	30 (1.0)	42 (1.6)	20 (0.7)
Moderate	5 (0.2)	5 (0.2)	12 (0.4)	10 (0.4)
Severe	0	1 (0.0)	4 (0.1)	0
Diarrhea	-	-	-	-
Any	309 (10.7)	323 (11.1)	269 (10.0)	205 (7.6)
Mild	251 (8.7)	264 (9.1)	219 (8.2)	169 (6.3)
Moderate	55 (1.9)	58 (2.0)	44 (1.6)	35 (1.3)
Severe	3 (0.1)	1 (0.0)	6 (0.2)	1 (0.0)
New or worsened muscle pain	-	-	-	-
Any	664 (22.9)	329 (11.3)	1055 (39.3)	237 (8.8)
Mild	353 (12.2)	231 (7.9)	441 (16.4)	150 (5.6)
Moderate	296 (10.2)	96 (3.3)	552 (20.6)	84 (3.1)
Severe	15 (0.5)	2 (0.1)	62 (2.3)	3 (0.1)
New or worsened joint pain	-	-	-	-
Any	342 (11.8)	168 (5.8)	638 (23.8)	147 (5.5)
Mild	200 (6.9)	112 (3.9)	291 (10.9)	82 (3.1)
Moderate	137 (4.7)	55 (1.9)	320 (11.9)	61 (2.3)
Severe	5 (0.2)	1 (0.0)	27 (1.0)	4 (0.1)
Use of antipyretic or pain medication	805 (27.8)	398 (13.7)	1213 (45.2)	320 (11.9)

N=number of subjects responding yes or no for any reaction within seven days of dosing.
n=number of subjects with the specified reaction.
Source: Adapted from Table 14.68 of C4591001 Interim Clinical Study Report.

Table 5. Frequency of Solicited Reactions Within Seven Days of each Dose (>55 Years)

-	**BNT162b2 Dose 1 N=2008 n (%)**	**Placebo Dose 1 N=1989 n (%)**	**BNT162b2 Dose 2 N=1860 n (%)**	**Placebo Dose 2 N=1833 n (%)**
Redness	-	-	-	-
Any (>2.0 cm)	106 (5.3)	20 (1.0)	133 (7.2)	14 (0.8)
Mild	71 (3.5)	13 (0.7)	65 (3.5)	10 (0.5)
Moderate	30 (1.5)	5 (0.3)	58 (3.1)	3 (0.2)
Severe	5 (0.2)	2 (0.1)	10 (0.5)	1 (0.1)
Swelling	-	-	-	-
Any (>2.0 cm)	141 (7.0)	23 (1.2)	145 (7.8)	13 (0.7)
Mild	87 (4.3)	11 (0.6)	80 (4.3)	5 (0.3)
Moderate	52 (2.6)	12 (0.6)	61 (3.3)	7 (0.4)
Severe	2 (0.1)	0	4 (0.2)	1 (0.1)
Pain at the injection site	-	-	-	-
Any	1408 (70.1)	185 (9.3)	1230 (66.1)	143 (7.8)
Mild	1108 (55.2)	177 (8.9)	873 (46.9)	138 (7.5)
Moderate	296 (14.7)	8 (0.4)	347 (18.7)	5 (0.3)
Severe	4 (0.2)	0	10 (0.5)	0
Fever	-	-	-	-
≥38.0°C	26 (1.3)	8 (0.4)	219 (11.8)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.1)	3 (0.2)	158 (8.5)	2 (0.1)
>38.4°C to 38.9°C	2 (0.1)	3 (0.2)	54 (2.9)	1 (0.1)
>38.9°C to 40.0°C	1 (0.0)	2 (0.1)	7 (0.4)	1 (0.1)
>40.0°C	0	0	0	0
Fatigue	-	-	-	-
Any	677 (33.7)	447 (22.5)	949 (51.0)	306 (16.7)
Mild	415 (20.7)	281 (14.1)	391 (21.0)	183 (10.0)
Moderate	259 (12.9)	163 (8.2)	497 (26.7)	121 (6.6)
Severe	3 (0.1)	3 (0.2)	60 (3.2)	2 (0.1)
Grade 4	0	0	1 (0.1)	0
Headache	-	-	-	-
Any	503 (25.0)	363 (18.3)	733 (39.4)	259 (14.1)
Mild	381 (19.0)	267 (13.4)	464 (24.9)	189 (10.3)
Moderate	120 (6.0)	93 (4.7)	256 (13.8)	65 (3.5)
Severe	2 (0.1)	3 (0.2)	13 (0.7)	5 (0.3)
Chills	-	-	-	-
Any	130 (6.5)	69 (3.5)	435 (23.4)	57 (3.1)
Mild	102 (5.1)	49 (2.5)	229 (12.3)	45 (2.5)
Moderate	28 (1.4)	19 (1.0)	185 (9.9)	12 (0.7)
Severe	0	1 (0.1)	21 (1.1)	0
Vomiting	-	-	-	-
Any	10 (0.5)	9 (0.5)	13 (0.7)	5 (0.3)
Mild	9 (0.4)	9 (0.5)	10 (0.5)	5 (0.3)
Moderate	1 (0.0)	0	1 (0.1)	0
Severe	0	0	2 (0.1)	0

-	**BNT162b2 Dose 1 N=2008 n (%)**	**Placebo Dose 1 N=1989 n (%)**	**BNT162b2 Dose 2 N=1860 n (%)**	**Placebo Dose 2 N=1833 n (%)**
Diarrhea	-	-	-	-
Any	168 (8.4)	130 (6.5)	152 (8.2)	102 (5.6)
Mild	137 (6.8)	109 (5.5)	125 (6.7)	76 (4.1)
Moderate	27 (1.3)	20 (1.0)	25 (1.3)	22 (1.2)
Severe	4 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain				
Any	274 (13.6)	165 (8.3)	537 (28.9)	99 (5.4)
Mild	183 (9.1)	111 (5.6)	229 (12.3)	65 (3.5)
Moderate	90 (4.5)	51 (2.6)	288 (15.5)	33 (1.8)
Severe	1 (0.0)	3 (0.2)	20 (1.1)	1 (0.1)
New or worsened joint pain	-	-	-	-
Any	175 (8.7)	124 (6.2)	353 (19.0)	72 (3.9)
Mild	119 (5.9)	78 (3.9)	183 (9.8)	44 (2.4)
Moderate	53 (2.6)	45 (2.3)	161 (8.7)	27 (1.5)
Severe	3 (0.1)	1 (0.1)	9 (0.5)	1 (0.1)
Use of antipyretic or pain medication	382 (19.0)	224 (11.3)	688 (37.0)	170 (9.3)

N=number of subjects responding yes or no for any reaction within seven days of dosing.
n=number of subjects with the specified reaction.
Source: Adapted from Table 14.68 of C4591001 Interim Clinical Study Report.

Reviewer Comment:

- *Three placebo recipients 16 to 55 years of age who reported fever of >42°C within seven days of the first or second dose were excluded from the analysis. As the subjects received placebo and these measurements were likely due to error, this is unlikely to affect safety conclusions.*

Unsolicited Safety

Table 6 presents the numbers and percentages of subjects ≥16 years of age who reported any unsolicited AE, SAE, AE leading to withdrawal, or death after the first dose. These numbers are reported for three separate risk windows: a) Dose 1 to one month post Dose 2 or unblinding (whichever is first), b) Dose 1 to six months post Dose 2 or unblinding (whichever is first), and c) (for placebo patients who received crossover vaccination) from crossover to March 13, 2021. The percentages of subjects reporting any SAE, AE leading to withdrawal, or death were generally similar between the vaccine and placebo groups from Dose 1 to one month after Dose 2 and from Dose 1 to six months after Dose 2 regardless of severity. A higher percentage of vaccine recipients reported any unsolicited AE after Dose 1 than placebo recipients. Four vaccine recipients reported SAEs up to six months post Dose 2 that were considered by the investigator to be related to the study intervention. In these analyses, 58.2% of study participants had at least four months of blinded follow-up after Dose 2.

A total of 19,525 subjects originally randomized to placebo received at least one dose of BNT162b2 after unblinding (Dose 3 and Dose 4) and before the March 13, 2021 data cutoff. Among these subjects, one (<0.1%) subject reported an SAE of anaphylactoid reaction after Dose 3 that was considered by the investigator to be related to the study intervention. Two subjects (<0.1%) died after receiving Dose 3, but neither were considered by the investigator to be related to the intervention.

Table 6. Number of Subjects ≥16 Years of Age Reporting at Least One AE by Time Period

-	**BNT162b2 1MPD2[a] N=21926 n (%)**	**Placebo 1MPD2[a] N=21921 n (%)**	**BNT162b2 6MPD2[b] N=21926 n (%)**	**Placebo 6MPD2[b] N=21921 n (%)**	**BNT162b2 PD3[c] N=19525[d] n (%)**
Any AE	6617 (30.2)	3048 (13.9)	6947 (31.7)	3568 (16.3)	4885 (25.0)
Related	5241 (23.9)	1311 (6.0)	5246 (23.9)	1313 (6.0)	4508 (23.1)
Severe	262 (1.2)	150 (0.7)	356 (1.6)	256 (1.2)	142 (0.7)
Life-Threatening	21 (0.1)	26 (0.1)	48 (0.2)	54 (0.2)	11 (0.1)
Any SAE	127 (0.6)	116 (0.5)	268 (1.2)	268 (1.2)	65 (0.3)
Related	3 (<0.1)	0	4 (<0.1)	1 (<0.1)	1 (<0.1)
Severe	71 (0.3)	66 (0.3)	148 (0.7)	156 (0.7)	37 (0.2)
Life-Threatening	21 (0.1)	26 (0.1)	48 (0.2)	54 (0.2)	11 (0.1)
Any AE leading to withdrawal	32 (0.1)	36 (0.2)	45 (0.2)	51 (0.2)	19 (0.1)
Related	13 (0.1)	11 (0.1)	13 (0.1)	12 (0.1)	12 (0.1)
Severe	10 (<0.1)	10 (<0.1)	10 (<0.1)	12 (0.1)	2 (<0.1)
Life-Threatening	3 (<0.1)	7 (<0.1)	15 (0.1)	16 (0.1)	4 (<0.1)
Death	3 (<0.1)	5 (<0.1)	15 (0.1)	14 (0.1)	2 (<0.1)

N=number of subjects who received at least one dose of the study intervention.
n=number of subjects reporting at least one event.
[a]*Includes all events from Dose 1 up to the earlier of one month post Dose 2 or unblinding.*
[b]*Includes all events from Dose 1 up to the earlier of six months post Dose 2 or unblinding.*
[c]*Includes all events from crossover vaccination (Dose 3) to March 13, 2021.*
[d]*Includes all subjects randomized to placebo who received BNT162b2 after unblinding.*
Source: Adapted from Tables 5, 7, and 14 of Summary of Clinical Safety.

Reviewer Comments:

- *The solicited and unsolicited AEs reported in the clinical study report were consistent with the Study Data Tabulation Model (SDTM) data.*
- *The solicited and unsolicited AE analyses presented do not include the 200 Human Immunodeficiency Virus (HIV)-positive participants. Similar safety results were observed in HIV-positive subjects.*
- *The imbalance in the frequencies of unsolicited AEs is driven largely by increased reactogenicity in the vaccine arm, in that many events associated with reactogenicity (e.g. injection site pain, fatigue, etc.) occurring within days of vaccination were reported as unsolicited AEs.*
- *Two subjects who received BNT162b2 and experienced an AE or SAE were not reported in the blinded follow-up safety analysis:*
    1. *One subject (C4591001 (b) (6)) received two doses of BNT162b2 and reported an SAE of acute hepatic failure on Day 100 that was not considered by the investigator to be related to the study intervention. The*

subject was unblinded and withdrew from the study on the same day that the SAE was reported. As the safety analyses included only events up to the day before unblinding (regardless of the reason for unblinding), this event was not considered to have occurred during blinded follow-up.

2. *One subject (C4591001 (b) (6)) received one dose of BNT162b2 and reported a case of tinnitus with unknown start and end dates.*

I defer to the clinical reviewer regarding the interpretation of these events.

- *The applicant stated that 58.2% of subjects in the unsolicited safety analysis completed at least four months of follow-up post Dose 2. Of note, it appears that the applicant considered a month to be equivalent to 28 days. The median follow-up from Dose 2 to six months post Dose 2 or unblinding among ≥16-year-old participants in the Safety Population was approximately 120 days.*
- *Ten subjects (six vaccine and four placebo) who received at least one dose of the study intervention were excluded from the Safety Set due to "lack of PI [Principal Investigator] oversight," which was not documented in the Statistical Analysis Plan. Among the six vaccine recipients, one non-serious AE of "excessive cerumen production" was reported that was not considered by the investigator to be related to the study intervention, and no SAEs were reported.*

Myocarditis and Pericarditis

One report of pericarditis was identified in a 66-year-old male participant 28 days after receiving Dose 2 of BNT162b2. One report of myocarditis was identified in a 25-year-old male participant in the placebo group five days after the second placebo dose.

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 were identified for the safety data during review. A higher percentage of subjects in the BNT162b2 group reported solicited local and systemic reactions than placebo recipients in both the younger (16 to 55 years) and older (>55 years) adult age groups after each dose. There were no major imbalances in reported SAEs, AEs leading to withdrawal, or deaths between the treatment groups at one month and up to six months after the second dose or unblinding/data cut-off.

10.2 Conclusions and Recommendations

There is evidence of reactogenicity associated with BNT162b2; the overwhelming majority of events were of mild or moderate severity and short duration. There was no evidence of increased risk of unsolicited SAE or death associated with BNT162b2 in Study C4591001. I defer to Drs. Susan Wollersheim and Ann Schwartz's clinical review memo on the overall safety conclusion for BNT162b2.