BLA Clinical Review Memorandum*

Application Type	Biologics License Application (BLA)
STN	125742/0
CBER Received Date	May 18, 2021
PDUFA Goal Date	January 16, 2022
Division / Office	DVRPA / OVRR
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Susan Wollersheim, MD Ann Schwartz, MD
Review Completion Date / Stamped Date	August 23, 2021
Supervisory Concurrence	Lucia Lee, M.D.; Team Leader CRB1/DVRPA/OVRR Maria Allende, M.D.; Chief, CRB1/DVRPA/OVRR
Applicant	BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)
Established Name	COVID-19 Vaccine, mRNA
(Proposed) Trade Name	COMIRNATY
Pharmacologic Class	Vaccine
Formulation, including Adjuvants	Each 0.3 mL dose contains 30ug modified mRNA encoding SARS-CoV-2 spike glycoprotein, encapsulated in lipid nanoparticles (LNP)
Dosage Form and Route of Administration	Suspension for intramuscular injection
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
Orphan Designated (Yes/No)	No

*Updated version of the previously uploaded memo corrected to add safety information to Sections 6.1.12. 2, 6.1.12.4, and 6.1.12.7 that was inadvertently omitted but does not change overall conclusions.

TABLE OF CONTENTS

GLOSSARY

AE	adverse event
AESI	adverse event of special interest
BLA	Biologics License Application
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease 2019
DVT	deep vein thrombosis
EUA	emergency use authorization
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
HIV	human immunodeficiency virus
IA	interim analysis
ICU	intensive care unit
IRC	Internal Review Committee
IRR	incidence rate ratio
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
MIS-A	multisystem inflammatory syndrome in children
MIS-C	multisystem inflammatory syndrome in adults
NAAT	nucleic acid amplification-based test
PD	protocol deviation
PE	pulmonary embolism
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PT	Preferred Term
PVP	Pharmacovigilance Plan
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	Standardised MedDRA Query
SOC	System Organ Class
Th1	T helper type 1
TTS	thrombosis with thrombocytopenia syndrome
US	United States
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VOC	variant of concern
VOI	variant of interest
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
WHO	World Health Organization

1. Executive Summary

BioNTech Manufacturing GmbH, Inc. submitted a Biologics License Application (BLA) for BNT162b2 (30 µg) vaccine (COMIRNATY) and is seeking an indication for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The primary immunization series consists of 2 intramuscular doses administered 3 weeks apart. BNT162b2 contains SARS-CoV-2 spike glycoprotein (S) antigens encoded in RNA formulated in lipid nanoparticles (LNPs). The structural elements of BNT162b2 are modified for translation of the antigen-encoding RNA. Encapsulation of the vaccine mRNA into LNPs has been done to (b) (4) .

Study C4591001, the main study to support the safety and efficacy of BNT162b2, is an ongoing multinational, randomized, clinical trial in a total of 44,165 participants (22,085 BNT162b2, 22,080 saline placebo) 16 years of age and older. A primary objective was to evaluate the efficacy of BNT162b2 to prevent laboratory-confirmed symptomatic COVID-19 occurring ≥7 days after Dose 2 in participants without serological or virological evidence of past SARS-CoV-2 infection before and during the vaccination regimen. The central laboratory nucleic acid amplification-based test (NAAT) result is used for the case definition, with a NAAT test that is authorized under FDA emergency use authorization (EUA). Vaccine efficacy (VE) against severe disease was evaluated as a secondary endpoint. Planned safety analyses included evaluation of: 1) local reactions, systemic events, and antipyretic/pain medication use from Day 1 through Day 7 after each dose in a subset of participants (approximately 4,900 per treatment group); 2) non-serious unsolicited adverse events from Dose 1 through 1 month after Dose 2 in all participants; 3) serious adverse events from Dose 1 through 6 months after Dose 2 in all participants; and deaths and related serious adverse events from Dose 1 through the end of the study in all participants.

Efficacy and safety data accumulated in the study through November 14, 2020, which included median follow-up of 2 months after Dose 2, supported FDA's December 11, 2020 issuance of an EUA for use of BNT162b2 in individuals 16 years of age and older. Following issuance of the EUA, study participants 16 years of age and older were progressively unblinded to their treatment assignment (when eligible for vaccination per national and local public health prioritization recommendations), and placebo recipients could choose to receive BNT162b2 with continued active unblinded follow-up in the study. This BLA submission included updated efficacy analyses of 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. The median follow-up after Dose 2 of all participants in the blinded placebo-controlled period was 4.3 months. Updated safety analyses included in the BLA submission evaluated data accumulated in both blinded and unblinded follow-up through March 13, 2021. The BLA safety database included >12,000 study participants originally randomized to BNT162b2 who completed least 6 months of total safety follow-up after Dose 2.

As of the March 13, 2021 data cutoff, the efficacy population 16 years of age and older who did not have evidence of SARS-CoV-2 infection through 7 days after the second dose included N=40,111 participants (19,993 BNT162b2, 20,118 placebo). The updated efficacy analyses showed that VE in preventing symptomatic COVID-19 occurring ≥7

days after Dose 2 was 91.1% [95% CI 88.8, 93.1]) in participants *without* evidence of SARS-CoV-2 infection and 90.9% (95%CI 88.5, 92.8) in participants *with or without* evidence of SARS-CoV-2 infection. These results were consistent with the VE in the protocol-specified event-driven final analyses that supported issuance of the EUA (VE 95% and 94.6%, respectively). The updated analyses of VE against severe COVID-19 in preventing symptomatic COVID-19 occurring ≥7 days after Dose 2 was 95.3% (95% CI: 71.0%, 99.9%) in participants *without* evidence of SARS-CoV-2 infection and 95.3% (95% CI: 70.9%, 99.9%) in participants *with or without* evidence of SARS-CoV-2 infection. SARS-CoV-2 variants of concern identified from COVID-19 cases in this study included B.1.1.7 (Alpha) and B.1.351 (Beta).

The safety population at the March 13, 2021 data cutoff included 22,026 BNT162b2 recipients and 22,021 placebo recipients 16 years of age and older. During the placebo-controlled phase, the most commonly reported solicited adverse reactions in the BNT162b2 group were pain, redness and swelling at the injection site, fatigue, and headache. Adverse reactions other than solicited reactogenicity events identified from the clinical trial data include lymphadenopathy in regional proximity to the vaccination site and potentially Bell's Palsy (the latter from a small numerical imbalance of temporally associated events). A slight imbalance in hypersensitivity-related events was observed during the trial, and hypersensitivity reactions have been reported during post-authorization use as well. There were otherwise no notable patterns between treatment groups for specific categories of serious or non-serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2. A total of 15 (0.2%) deaths in vaccine recipients and 14 (0.2%) in placebo recipients were reported during blinded, placebo-controlled follow-up, and an additional 6 deaths were reported during unblinded follow-up following vaccination with BNT162b2; none of these deaths were assessed to be related to vaccination. A total of 42 pregnancies were reported by BNT162b2 recipients from Dose 1 through the data cutoff date. The frequencies of spontaneous abortion, miscarriage, and elective abortion were similar between the vaccine and the placebo groups.

Post-authorization safety surveillance has identified two rare but serious adverse reactions: anaphylaxis and myocarditis/pericarditis. The risk of anaphylaxis associated with BNT162b2 appears to be similar in magnitude to the risk of anaphylaxis following approved preventive vaccines in general and can be managed with standard vaccination practices. The risk of myocarditis/pericarditis appears to be greatest in individuals under the age of 40, in particular in males following Dose 2, and increased with decreasing age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae.

To address the identified risk of myocarditis/pericarditis, FDA conducted a quantitative, age- and sex-stratified benefit-risk analysis, using healthcare claims and CDC surveillance databases, to evaluate the balance of vaccine benefits (prevention of COVID-19 hospitalizations, intensive care unit admissions and deaths) against excess risk of myocarditis/pericarditis under various conditions of COVID-19 incidence and vaccine effectiveness informed by real-world data. These analyses supported that based on current understanding of vaccine-associated myocarditis/benefits of vaccination would outweigh risks of myocarditis/pericarditis for individuals 16 years of

age and older under all conditions examined. Mitigation of the observed risks of myocarditis/pericarditis and associated uncertainties will be accomplished through labeling (including warning statements about the risks of vaccine-associated myocarditis/pericarditis) and through continued safety surveillance and postmarketing studies to be conducted by the Applicant, US government agencies (including FDA and CDC), and other healthcare stakeholders.

The clinical data submitted exceed FDA's expectations for data to support licensure of vaccines for prevention of COVID-19, including relevant efficacy success criteria and numbers of vaccinated study participants and follow-up time (i.e., at least 3,000 vaccinated participants in each age group with at least 6 months of total safety follow-up) for an acceptable safety database. The clinical data submitted in this application, together with the quantitative benefit-risk assessment summarized in this review, support approval of BNT162b2 for the indication of active immunization to prevent symptomatic coronavirus disease 2019 (COVID 19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

Pediatric studies of BNT162b2 in children <16 years of age, as required by the Pediatric Research Equity Act, were deferred for this application and will be completed after approval of BNT162b2 for use in individuals 16 years of age and older. The Applicant also committed to conduct additional postmarketing safety studies, including the assessment of pregnancy and infant outcomes following immunization with BNT162b2 during pregnancy.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The table below summarizes demographic representation of study participants who enrolled in the Phase 2/3 portion of the ongoing study C4591001 and were randomized to a two-dose series of BNT162b2 or placebo.

Table 1. Randomized Participants by Subgroup, Study C4591001

Subgroup	BNT162b2	Placebo	Total
Age (≥16 years)	22085	22080	44165
16-55 years	13104	13132	26236
>55 years	8981	8948	17929
16-17 years	378	377	755
Gender			
Male	11357	11127	22484
Female	10728	10953	21681
Ethnicity			
Hispanic/Latino	5715	5710	11425
Non- Hispanic/Non-Latino	16259	16256	32515
Not reported	111	114	225
Race			
White	18106	18105	36211
Black/African American	2106	4232	4232
All others	1873	1849	3722

Source: FDA-generated table.

The demographic characteristics of the evaluable efficacy population of 42,244 participants was 83% White, 50.9% male, and 74.7% non-Hispanic/non-Latino ethnicity. The younger age group (16-55 years of age) represented 55.8% of the total evaluable efficacy population, while participants >55 years of age represented 39.5% of the total.

Subgroup analyses of vaccine efficacy (although limited by small numbers of cases in some subgroups) did not suggest meaningful differences in efficacy across genders, ethnic groups, geographies, or for participants with obesity or medical comorbidities associated with high risk of severe COVID-19.

The overall safety population was 49.1% female, 50.9% males, 25.6% Hispanic/Latino, 82.0% White, 9.6% African American, 4.3% Asian, <3% other racial groups. The median age was 51 years, and 20.8% were older than 65 years old. The most frequently reported comorbidities were obesity (35.1%), diabetes without chronic complications (7.8%) and chronic pulmonary disease (7.8%). Geographically, enrollment included individuals from the United States (US; 76.5%), Argentina (15.3%), Brazil (6.1%), South Africa (2.0%), Turkey (1.0%), and Germany (1.0%). In safety analyses, reported rates of solicited local and systemic ARs and antipyretic/pain medication use in the 7 days after BNT162b2 vaccinations were generally lower among older adults (>55 years of age) compared with younger adults and adolescents (16-55 years of age). Other differences between the age groups in overall rates and types of unsolicited AEs and SAEs largely reflected differences in underlying medical conditions between the respective age groups (as these AEs were assessed as related to the underlying medical conditions rather than to the vaccine). No clinically meaningful differences in the occurrence of solicited AEs, unsolicited AEs or SAEs were observed by, ethnicity, race, or sex subgroups.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	N/A

Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

COVID-19 is an infectious disease caused by SARS-CoV-2, a novel, zoonotic coronavirus, which can cause severe respiratory symptoms, pneumonia, respiratory failure, multi-organ failure, and death. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome, leading to multiorgan failure and death. Elderly individuals (in particular men >60 years of age) and those with several underlying medical conditions, including obesity, diabetes, asthma, chronic kidney disease, hypertension, and immunosuppression, have been reported to be at increased risk for severe illness from COVID-19. Multisystem inflammatory syndrome in both children (MIS-C) and adults (MIS-A) is a rare but serious COVID-19-associated condition that can present with persistent fever, laboratory markers of inflammation and heart damage, and, in severe cases, hypotension and shock (CDC 2021a; CDC Advisory Committee on Immunization Practices 2021a).

The first recorded COVID-19 cases were reported in December 2019 in Wuhan, China. During January 2020 cases were reported from several other countries, including the United States. The first case report of novel coronavirus 2019 (2019-nCov) in the United States was published on January 31, 2020 in the New England Journal of Medicine (Holshue et al. 2020). On January 31, 2020, the United States Secretary of Health and Human Services 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to present a challenge to global health and, at the time of this review, has caused approximately 209 million cases of COVID-19, including 4.4 million deaths worldwide (World Health Organization 2021a). In the United States (US), more than 37 million cases have been reported to the Centers for Disease Control and Prevention (CDC), of which 90% have occurred in individuals 16 years of age or older. While the pandemic has caused morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2 and variants has caused significant challenges and disruptions worldwide to healthcare systems, economies, and many aspects of human activity (travel, employment, education). Socioeconomic effects of the pandemic are exacerbating health and societal disparities that disproportionately affect historically disadvantaged groups, and appear to be leading to widening inequality (CDC 2021b).

As such, the COVID-19 pandemic has disproportionately affected individuals of racial and ethnic minority groups, including African American and Hispanic/Latino groups (CDC 2021c).

The emergence of SARS-CoV-2 variants with multiple mutations in the SARS-CoV-2 spike (S) protein in India (B1.617 lineage [B1.617.2 delta variant]), the United Kingdom (B.1.1.7 lineage [alpha variant]), Brazil (P.1 lineage [gamma variant]), and South Africa (B.1.351 lineage [beta variant]), has raised concerns regarding increased transmission rates; at the time of this review, these variants of concern account for 82.2%, 9.0%, 3.8% and 0.1%, respectively, of SARS-CoV-2 lineages circulating in the US (CDC 2021d).

Since December 2020, COVID-19 vaccines have been available in the United States under EUA. As of August 15, 2021, among more than 168 million fully vaccinated individuals in the U.S., 6,239 hospitalizations and 1,263 deaths due to vaccine breakthrough have been reported by passive surveillance. Of hospitalized or fatal breakthrough cases, 74% occurred among individuals 65 years of age and older. Despite the occurrence of breakthrough cases in vaccinated individuals, according to current data, vaccination elicited protection against severe disease, hospitalization, and death remains high. COVID-19 cases, and in particular severe cases, hospitalizations, and deaths, remain overwhelmingly among unvaccinated individuals. Increasing representation of vaccinated individuals among mild to moderate COVID-19 cases is likely due in part to increasing uptake of the vaccine (which is not 100% protective), although waning immunity and/or decreased vaccine effectiveness against the delta variant may be contributing. Surveillance is ongoing to assess the impact of new variants on vaccine effectiveness. Vaccine clinical research and epidemiological surveillance are ongoing to assess durability of protection and parameters to determine whether and when there would be a need for a booster dose.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Remdesivir is the only product currently approved by the FDA for use in adults and pediatric patients 12 years of age and older for treatment of COVID-19 requiring hospitalization. Prior to its approval, remdesivir was authorized for emergency use in adults and pediatric patients and remains authorized for emergency use in hospitalized pediatric patients who are not included in the indicated population under licensure.

Emergency use authorizations of COVID-19 pharmacological products for post-exposure prophylaxis and/or treatment of COVID-19 are as follows:

Table 2. Emergency Use Authorized Pharmacological Products for Post-exposure Prophylaxis and/or Treatment of COVID-19

Product	Date of EUA	Authorized Use and Population
SARS-CoV-2-targeting Monoclonal Antibodies • Bamlanivimab/etesevimab • Sotrovimab • Casirivimab/imdevimab	Reissued February 25, 2021 May 26, 2021 Reissued July 30, 2021	All three products are indicated for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years and older at high risk for progressing to severe COVID-19[a] Casirivimab/imdevimab is also authorized for post-exposure prophylaxis (prevention) for COVID-19 in patients at high risk for progressing to severe COVID-19[b]
Antiviral Drugs • Remdesivir	Reissued October 22, 2020 (following FDA approval in adults and some pediatric patients)	Treatment of COVID-19 in hospitalized pediatric patients weighing at least 3.5 kg to <40 kg, or <12 years of age weighing at least 3.5 kg, or ≥12 years and weighing at least 40 kg
Immune Modulators • Baricitinib • Actemra	11/19/2020 06/24/2021	Treatment of COVID-19 in hospitalized patients[b] receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO
COVID-19 Convalescent Plasma	Reissued March 9, 2021	Treatment of hospitalized patients with COVID-19

[a] Indicated for adults and pediatric patients 12 years of age and older weighing at least 40 kg
[b] Indicated for adults and pediatric patients 2 years and older
ECMO extracorporeal membrane oxygenation, EUA emergency use authorization
Source: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs Accessed August 2, 2021.

2.3 Safety and Efficacy of Pharmacologically Related Products

At present, no vaccine is approved by the FDA for prevention of COVID-19. The FDA has issued EUAs for three COVID-19 vaccines to mitigate the SARS-CoV-2 pandemic.

Table 3. Emergency Use Authorized Vaccines to Prevent COVID-19

Applicant	Regimen	Population	Date of EUA and Amendments
Pfizer/BioNTech	2 doses 3 weeks apart	Individuals ≥16 years of age Individuals ≥12 years of age	December 11, 2020 EUA Amendment: May 10, 2021
Pfizer/BioNTech	3rd dose	Certain immunocompromised[a] individuals ≥12 years of age	EUA Amendment: August 12, 2021
Moderna	2 doses 4 weeks apart	Adults ≥18 years of age	December 18, 2020
Moderna	3rd dose	Certain immunocompromised[a] individuals ≥18 years of age	EUA Amendment: August 12, 2021
Janssen	Single dose	Adults ≥18 years of age	February 27, 2021

[a] Solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Moderna COVID-19 mRNA vaccine

In an ongoing Phase 3 study that enrolled participants ≥18 year of age (n=~14,000 vaccine, n=~14,000 placebo), VE was 94.1% to prevent PCR-confirmed COVID-19 occurring at least 14 days after completion of a 2-dose regimen. Common solicited adverse reactions after vaccination were injection site reactions, headache, fatigue, muscle aches, and nausea, which were generally mild to moderate and lasted 1-2 days (FDA 2020a). At the time of this review, more than 142 million doses of the Moderna COVID-19 vaccine have been administered in the US (CDC 2021). Consistent with Phase 3 trials, real-world efficacy of mRNA vaccines has been demonstrated to be about 90% (Pawlowski et al. 2021; Thompson et al. 2021). During post-EUA surveillance myocarditis and pericarditis, and rare cases of anaphylaxis, were reported after vaccination (CDC 2021e).

Janssen COVID-19 replication-incompetent human adenovirus serotype 26 (Ad26) vector vaccine

In an ongoing Phase 3 study that enrolled participants ≥18 year of age (n=~20,000 vaccine, n=~20,000 placebo), VE was 66.9% to prevent laboratory-confirmed, moderate-severe COVID19 occurring at least 14 days after a single dose. Common solicited adverse reactions were injection site pain, headache, fatigue, and myalgia, which were mostly mild and moderate. In the post-EUA surveillance period, thrombosis with thrombocytopenia syndrome (TTS) and Guillain-Barré syndrome were identified as rare, but serious adverse reactions following vaccination (CDC Advisory Committee on Immunization Practices 2021b).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Clinical trial experience

EUA of the Pfizer-BioNTech COVID-19 Vaccine (also referred to as BNT162b2) was based on the following data: In individuals ≥16 years of age enrolled in a Phase 2/3 portion of an ongoing study (n= ~22,000 vaccine, n=~22,000 placebo), vaccine efficacy (VE) was 95% to prevent PCR-confirmed COVID-19 occurring at least 7 days after completion of a 2-dose regimen. Common solicited adverse reactions after vaccination were injection site reactions, fatigue, headache, muscle pain, chills, and joint pain, which were generally mild to moderate and lasted a few days. Vaccine effectiveness in participants 12-15 years of age (n=1,131 vaccine, n=1,129 placebo) was inferred by

immunobridging, based on a comparison of SARS-CoV-2 50% neutralization antibody titers (SARS-CoV-2 mNG microneutralization assay) at 1 month after Dose 2, to participants 16-25 years of age, and supported by a supplemental efficacy analysis showing VE after 7 days post Dose 2 was 100% (95% CI 75.3; 100.0) without prior evidence of SARS-CoV-2 infection and 100% in participants with or without prior infection (FDA 2020b).

Post-EUA

As discussed in more detail above, since the issuance of the EUA, published observational studies have supported the effectiveness of BNT162b2 to prevent COVID-19, including high-level protection against severe disease, hospitalization, and death, although recent evidence suggests some decrease in vaccine effectiveness against mild to moderate disease since emergence of the delta variant in the US (CDC 2021f).

During the post-EUA surveillance period, cases of myocarditis and pericarditis were reported after vaccination, as well as rare cases of anaphylaxis (CDC Advisory Committee on Immunization Practices 2021c; CDC 2021e).

Please see CBER pharmacovigilance reviewer's memorandum for details about the Applicant's ongoing post-authorization studies and results of cumulative analysis of post-authorization AE reports received through February 28, 2021.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Prior to BLA submission

- EUA 27034
  - November 20, 2020: Submission of EUA request for individuals ≥16 years of age
  - December 11, 2020: Issuance of EUA for individuals ≥16 years of age
  - April 9, 2021: Submission of EUA request for individuals 12-15 years of age
  - May 10, 2021: Issuance of EUA for individuals 12-15 years of age
  - June 25, 2021: EUA amendment to include warning statement and associated information regarding myocarditis and pericarditis in the Fact Sheet for Vaccination Providers and the Fact Sheet for Recipients and Caregivers

- Major pre-submission BLA-associated regulatory activity
  - April 22, 2020: IND 19736 submission, first subject enrolled on April 29, 2020
  - June 11, 2020-July 6, 2020 Type C Meeting to discuss clinical development program, including revised Phase 1/2/3 Study C4591001 intended to support licensure
  - July 7, 2020: Fast Track Designation granted for individuals ≥18 years of age
  - November 18, 2020-April 2, 2021 Request for Comments and Advice re: Study C4591001 Placebo Participants
  - March 31, 2021: Pre-BLA meeting (chemistry, manufacturing, and controls [CMC])
  - March 9, 2021: Pre-BLA meeting (clinical)
  - April 16, 2021: plans for rolling BLA submission agreed upon between CBER and the Applicant

- Major post-submission BLA regulatory activity
  - July 15, 2021: Priority review granted

2.6 Other Relevant Background Information

Relevant FDA guidance

In June 2020, FDA published guidance on the Development and Licensure of Vaccines to Prevent COVID-19 (FDA 2020c). In October 2020, FDA published guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 (revised February 2021) (FDA 2021a).

Vaccines and Related Biological Products Advisory Committee (VRBPAC) meetings

- On October 22, 2020, a VRBPAC meeting was held to discuss considerations for development, EUA and licensure of vaccines to prevent COVID-19. The VRBPAC committee endorsed the principles outlined in the June and October FDA guidance documents regarding safety and effectiveness data to support EUA and licensure and expectations for continued post-authorization and post-approval evaluation of COVID-19 vaccines.

- On December 10, 2020, a VRBPAC meeting was held to discuss Pfizer-BioNTech's EUA request for their vaccine to prevent COVID-19 in individuals 16 years of age and older. The committee voted in favor of a determination that, based on the totality of scientific evidence available, the benefits of the vaccine outweighed its risks for use in individuals 16 years of age and older.

  Discussion topics included: (a) Pfizer-BioNTech's plan for an unblinded, placebo-controlled follow-up in ongoing trials, in the event that the vaccine were made available under EUA. Study participants 16 years of age and older were then progressively unblinded to their treatment assignment (when eligible per local recommendations), and placebo recipients could choose to receive BNT162b2; (b) scientific knowledge gaps and considerations for evaluation of vaccine safety and effectiveness in populations who would receive the Pfizer-BioNTech COVID-19 Vaccine under an EUA: the VRBPAC committee commented on the need to further assess vaccine effect on asymptomatic infection and viral shedding, and further evaluation of safety and effectiveness in subpopulations such as individuals with HIV and individuals with prior exposure to SARS-CoV-2.

- An emerging signal for myocarditis and pericarditis following mRNA COVID-19 vaccines was discussed at FDA VRBPAC and CDC Advisory Committee on Immunization Practices meetings held on June 10, 2021. Based on the strength of evidence for a causal association, the Pfizer-BioNTech COVID-19 Vaccine EUA Fact Sheet was revised on June 25, 2021 to add a Warning for myocarditis and pericarditis, and the Pharmacovigilance Plan (PVP) was amended to include myocarditis and pericarditis as important identified risks.

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 clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Sponsor responsibilities were transferred from BioNTech SE to Pfizer Inc. for the conduct of clinical study C4591001, including compliance with Good Clinical Practice as per 21 CFR 312. Bioresearch Monitoring inspections of nine clinical sites in study C4591001 did not identify deficiencies that would affect the integrity of the clinical data submitted in this BLA.

3.3 Financial Disclosures

Studies C4591001 and BNT162-01 Disclosure start date: April 29, 2020. Disclosure Cut-off Date: March 25, 2021
Was a list of clinical investigators provided? ☑ Yes ☐ No
Total number of investigators identified: 1834
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 4 Is an attachment provided with details of the disclosable financial interests/arrangements? ☑ Yes ☐ No Is a description of the steps taken to minimize potential bias provided? ☑ Yes ☐ No
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 4 Is an attachment provided with the reason? ☑ Yes ☐ No

The investigators with disclosable financial interests represented 0.4% (n=7/1,834) of the total investigators who participated in covered clinical studies.

Efforts reported to eliminate bias for the covered studies consisted of the following:

- Randomized, double-blind and multicenter study design as well as pre-specified statistical methods as per the statistical analysis plan
- Frequent monitoring of investigator trial sites and auditing of study sites
- Validity of data collected was confirmed by standard monitoring procedures
- Data processing involved cleaning checks (querying data through electronic edit checks) to ensure that errors were identified and corrected
- Data were reviewed by clinicians and queries were generated in case of inconsistencies during the course of the trial
- The study report underwent review by the project team and Quality Control; and

- Study sites performing safety evaluations were determined acceptable based on appropriate certification or historical performance and/or qualifications and credentials.

  Reviewer Comment: The Applicant satisfactorily addressed possible study investigator financial interests that could impact clinical data quality.

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

4.1 Chemistry, Manufacturing, and Controls

The CBER CMC reviewer identified no issues that would impact the conclusions of the clinical review.

4.2 Assay Validation

Two clinical diagnostic assays were used to assess clinical endpoints in pre-licensure clinical trials. The information provided in the BLA supported the suitability of Cepheid Xpert Xpress assay and Roche Elecsys Anti-SARS-CoV-2 assay for their intended uses to detect SARS-CoV-2 in clinical specimens and to determine serostatus to SARS-CoV-2, respectively.

4.3 Nonclinical Pharmacology/Toxicology

The CBER toxicology reviewer identified no issues in preclinical studies that would affect clinical review of the submitted interim clinical study reports, and based on current hypotheses regarding the etiology of vaccine-associated enhanced disease, the preclinical data provided in the BLA are reassuring due to: (1) the robust induction of functional (i.e., neutralizing) antibodies in mice and rhesus macaques; (2) the T helper type 1 (Th1) bias in T cell responses; and (3) the lack of disease in vaccinated rhesus macaques challenged with SARS-CoV-2. The nonclinical absorption, distribution, metabolism, and excretion studies indicate that the LNP mainly localizes to the site of injection and, to a lesser extent, distributes to the liver. Please see CBER toxicology review memorandum for further details.

4.5 Statistical

No major statistical issues were identified by CBER statistical reviewers in this application. The key statistical analyses for safety and efficacy were confirmed by CBER statistical reviewers.

4.6 Pharmacovigilance

Post-EUA safety surveillance reports received by FDA and CDC identified two rare but clinically important serious adverse reactions: anaphylaxis and myocarditis/pericarditis. The crude reporting rate for anaphylaxis in the Vaccine Adverse Event Reporting System (VAERS), including unconfirmed and potentially duplicate reports, has been ~6 cases per million doses, which is similar in magnitude to rates of anaphylaxis reported for other preventive vaccines. Reporting rates for medical chart-confirmed myocarditis/pericarditis in VAERS have been higher among males under 40 years of age than among females and older males and have been highest in males 12-17 years of age (~65 cases per million doses administered as per CDC communication on August 20, 2021). Although some cases of vaccine-associated myocarditis/pericarditis required intensive care support (with several suspected fatal cases under CDC

investigation but not confirmed at the time of this review), available data from short-term follow-up suggest that most individuals affected by vaccine-associated myocarditis/pericarditis have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals.

Anaphylaxis will be monitored through routine pharmacovigilance activities, including a data capture aid to identify relevant clinical information, and post-licensure safety studies. Mitigation of the observed risks of myocarditis/pericarditis and associated uncertainties will be accomplished through labeling (including warning statements about the risks of vaccine-associated myocarditis/pericarditis) and through continued safety surveillance and postmarketing studies conducted by the Applicant, by public health agencies within the US government (including FDA and CDC), and by other healthcare stakeholders. Please see CBER PVP review memorandum for further details.

4.7 Risk-Benefit Assessment

FDA conducted a quantitative benefit-risk assessment to inform the review of Pfizer and BioNTech's Biological Licensure Application (BLA) for use of mRNA COVID-19 vaccines in individuals 16 years of age and older. The assessment evaluated the benefits and risks per million individuals who complete vaccination with two doses of BNT162b2. The analysis was conducted for the groups stratified by combinations of sex and age (12-15, 16-17, 18-24, and 25-29 years). The model assessed the benefits of vaccine-preventable COVID-19 cases, hospitalizations, ICU visits and deaths, and the risks of vaccine-related excess myocarditis/pericarditis cases, hospitalizations, and deaths. The major sources of data included age/sex specific COVID-19 case and hospitalization incidences reported on COVID NET on July 10, 2021, the myocarditis/pericarditis case rate attributable to vaccine obtained from the OPTUM database, and the vaccine related myocarditis/pericarditis deaths reported through VAERS. The assessment constructed scenarios for both the most likely short-term moving direction of the pandemic and the worst case, which used the most conservative assumptions for all model inputs.

The most likely scenario assumed vaccine protection duration of 6 months, 10x COVID-19 case incidence and 4x COVID-19 hospitalization incidence as compared with those of July 10 (recent nadir), 70% vaccine efficacy against COVID-19 case, 80% vaccine efficacy against hospitalization, and no vaccine-related myocarditis death. The model results indicate that, for all age/sex groups and across all model outcomes, the benefits clearly outweigh the risks. For males 16-17 years old—the group with the highest risk of myocarditis/pericarditis—the model predicts that prevented COVID cases, hospitalizations, ICU admissions, and deaths are 136,000, 506, 166 and 4 per million vaccinated individuals, respectively. The excess myocarditis/pericarditis cases, associated hospitalizations, and deaths attributable to vaccine are 196, 196, and 0 per million vaccinated individuals, respectively.

The worst-case scenario used the most conservative assumptions for all the model inputs and assumed protection against COVID-19 over 6 months post-vaccination, the COVID-19 case and hospitalization incidences as of July 10, 2021, 70% vaccine efficacy against COVID-19 case, 80% vaccine efficacy against COVID-19 hospitalization, and 0.002% myocarditis/pericarditis death rate. For males 16-17 years old, the model predicted that prevented COVID cases, hospitalizations, ICU admissions, and deaths are 14,000, 127, 41, and 1 per million vaccinated individuals in this age group,

respectively. The excess myocarditis/pericarditis cases and associated hospitalizations and deaths attributable to the vaccine are 196, 196, and 0 per million vaccinated individuals in this age group, respectively. Even with the conservative assumption on the myocarditis/pericarditis death rate, the model predicted 0 deaths associated with myocarditis/pericarditis. The model predicts a higher number of myocarditis/pericarditis-related hospitalizations compared to prevented COVID-19 hospitalizations. However, considering the differential clinical outcomes of the hospitalization from two difference causes, FDA considers the benefits of the vaccine still outweigh the risks for the highest risk group, males 16-17 years old, under this worst-case scenario.

The benefit-risk estimates are limited by uncertainties associated with the dynamics of pandemics. The major uncertainties in benefits are related to potential changes in COVID-19 incidence over time and vaccine efficacy and duration of protection in the face of emerging virus variants. The major risk uncertainty is the data on vaccine-related myocarditis cases and deaths.

For further details, please refer to the review memorandum from the Analytics and Benefit-Risk Assessment Team, Office of Biostatistics and Epidemiology, CBER.

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

5.1 Review Strategy

Clinical data that were available as of November 14, 2020 from Phase 1 study BNT162-01 and Phase 1/2/3 study C4591001 participants ≥16 years of age enrolled by October 9, 2020 were submitted and reviewed by FDA. See the EUA Memorandum for the Pfizer COVID-19 Vaccine.

This BLA contains new clinical data, as follows:

Study C4591001

- Phase 1
  For BNT162b2 (30 µg), for participants ages 18-55 years (inclusive) and 65-85 years (inclusive):
  - Safety to approximately 6 months after Dose 2 (cutoff date: March 13, 2021)
  - Immunogenicity at 6 months after Dose 2 (adults 18-55 years of age only)

- Phase 2/3
  For participants 16-55 years and >55 years of age:
  - Safety to ≥6 months after Dose 2, comprised of participants in the blinded placebo-controlled and/or open-label follow-up period
  - Efficacy for all participants in the efficacy analysis populations (i.e., ≥12 years of age) with confirmed COVID-19 cases up to March 13, 2021.

Study BNT162-01

BNT162b2 by dose level (1 to 30 µg) for participants 18-85 years of age:

- Safety to 1 month after Dose 2
- Immunogenicity: neutralizing antibody titers up to 42 days after Dose 2, T-cell responses up to ~6 months after Dose 2 (18-55 years of age: all dose levels; 56-85 years of age: 20-µg dose level only)

Only safety and efficacy data in individuals 16 years of age and older, the population for intended use, who received the final vaccine formulation (BNT162b2 30 µg) are presented in this clinical memorandum.

Because the primary source of pre-licensure study data to support vaccine safety and effectiveness is a single study, C4591001, FDA agreed with the Applicant's proposal not to include integrated summaries of efficacy or safety in the BLA submission. Consequently, the sections of the clinical memo usually reserved for review of these integrated summaries (Sections 7 and 8) are not applicable.

Post-authorization effectiveness data from observational studies referenced in Section 2 and Section 11 are limited to published literature and were not submitted as part of the licensure application. Therefore, FDA has not independently reviewed and confirmed the data or assessed the study designs for potential sources of bias.

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

The primary source of data considered for review of this investigational vaccine were documents submitted to STN 125742/0. The following sections were reviewed in support of this application:
Module 1, all sections: Administrative Information and Prescribing Information
Section 2.2 Introduction
Section 2.5 Clinical Overview
Section 2.7.3 Summary of Clinical Efficacy
Section 2.7.4 Summary of Clinical Safety
Section 2.7.6 Synopses of Individual Studies
Section 5.2 Tabular Listing of All Clinical Studies
Section 5.3.5.1 Clinical Study Reports

During the BLA review period, the Applicant submitted a total of 35 amendments in response to CBER's requests for clinical information.

Table 4. Amendments to the Original BLA 125742/0 (submitted May 6, 2021)

Amendment Number	Date Submitted	Description
1	May 18, 2021	Second roll of the BLA
2	May 19, 2021	Request for proprietary name review
3	May 19, 2021	Response to May 18, 2021 comments re: datasets
5	June 7, 2021	COVID-19 cases: strain sequencing data
6	June 16, 2021	Response to June 8, 2021 comments re: datasets, label
7	June 17, 2021	Response to June 9, 2021 comments re: PREA deferred studies
8	July 2, 2021	Response to June 29, 2021 comments re: latest date of randomization for study C4591001 participants in the reactogenicity subset
9	July 2, 2021	Response to June 25, 2021 comments re: solicited local reactions frequencies, by severity, in study BNT162-01 participants
12	July 16, 2021	Response to July 6, 2021 comments re: HIV cohort: severe AEs and AEs leading to study withdrawal
15	July 23, 2021	Response to July 15 and 20, 2021 comments re: study C4591007 goal dates and revised pediatric plan

Amendment Number	Date Submitted	Description
17,18, 28	July 26, 2021 July 28, 2021 August 2, 2021	Responses to Q1-2, 3-5 of July 22, 2021 comments re: shell tables and other clinical comments
22	July 30, 2021	Response to July 27, 2021 comments re: vaccine effectiveness
23	July 30, 2021	Response to July 26, 2021 comments re: disposition of pregnant participants
26	August 2, 2021	Response to July 29, 2021 comments re: safety analysis by age
27	August 2, 2021	Response to July 28, 2021 comments for package insert
30	August 3, 2021	Response to July 28, 2021 comments re: post marketing observational safety studies to assess myocarditis/pericarditis
32	August 5, 2021	Response to August 3, 2021 comment regarding excluding a case from the efficacy analyses
37	August 9, 2021	Response to comment 6 of July 22, 2021 request re: shell tables (efficacy)
38	August 9, 2021	Response to August 5, 2021 comments for package insert
45	August 12, 2021	Response to August 9, 2021 comments re: sequencing data
49	August 16, 2021	Response to August 13, 2021 comments for package insert
51	August 16, 2021	Response to August 13, 2021 comments re: safety-related PMR/PMC studies
52	August 16, 2021	Response to August 13, 2021 comments re: duration of follow up for the efficacy population
58	August 18, 2021	Response to August 17, 2021 comments for package insert
59, 67, 69	August 18, 2021 August 19, 2021 August 20, 2021	Response to August 17 and 19, 2021 comments re: PMC/PMR commitments received in Amendment 51
66	August 19, 2021	Response to August 18, 2021 comments for package insert
68	August 20, 2021	Response to August 19, 2021 comments for package insert
71	August 20, 2021	Response to August 20, 2021 comments re: package insert
72	August 20, 2021	Response to August 20, 2021 comments re: shell table for unsolicited AEs
74	August 21, 2021	Response to August 21, 2021 comments for package insert
75	August 21, 2021	Response to August 21, 2021 comments re: PMR/PMC studies and final study protocol date for study C4591007

Source: FDA-generated table.

The amendments satisfactorily addressed all clinical requests sent during the review period, and salient responses from the amendments were incorporated into this memorandum.

Supportive information from EUA 27034/0 and clinical study protocols reviewed under IND 19736 were also referenced during the review cycle.

5.3 Overview of Clinical Studies

Interim reports from two ongoing clinical studies were submitted to support approval and licensure of Pfizer-BioNTech COVID-19 Vaccine (BNT162b2). Study C4591001 is a multicenter, multinational Phase 1/2/3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study. Study BNT162-01 is a Phase 1 study that

evaluated various vaccine candidates and dose levels for differing formulations of the vaccine.

Table 5. Overview of Clinical Studies

Study Number	Description	BNT162b2 (30 µg)* Group Phase, Number of Participants, Country	Placebo Group Phase, Number of Participants, Country	Study Status
C4591001	Phase 1,2,3 randomized, placebo-controlled, observer-blind; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Phase 1[a]: 24 (USA) Phase 2/3[b]: 22085 Argentina: 2887 Brazil:1452 Germany: 250 South Africa: 401 Turkey: 251 USA: 16844	Phase 1[a]: 6 (USA) Phase 2/3[b]: 22080 Argentina: 2889 Brazil:1448 Germany: 250 South Africa: 399 Turkey: 249 USA: 16845	Ongoing
BNT162-01	Phase 1/2 randomized, open-label; to evaluate safety and immunogenicity, dose escalation	Phase 1: 24 (Germany)	0	Ongoing

Source: STN 125742.037 c4591001-508-safety tables
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 18-55 years and 56-85 years); Phase 3: enrolled individuals ≥16 years of age (stratified as 16-55 years and >55 years).

5.4 Consultations

For the purpose of informing the design of required postmarketing safety studies and pediatric clinical trials as required by PREA, FDA cardiologists from the Center for Drug Evaluation and Research were asked to provide recommendations for diagnostic evaluations and monitoring for myocarditis/pericarditis (including feasibility of routine screening tests for subclinical myocarditis), interpretation of cardiac testing, and follow-up of identified clinical and subclinical cases. FDA incorporated these recommendations into negotiations with the Applicant on postmarketing studies.

5.4.1 Advisory Committee Meeting

The most critical issues involving data to support safety and effectiveness of this vaccine were covered in the October 2020, December 2020, and June 2021 VRBPAC meetings. More complete information concerning the risk of myocarditis/pericarditis became available during the BLA review as post-EUA surveillance and observational studies. FDA's assessment of this information did not impact the overall benefit/risk considerations to an extent that VRBPAC input was needed to guide a licensure decision for use in individuals ages 16 years and older.

5.5 Literature Reviewed

CDC, 2021, COVID-19 Vaccinations in the United States. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total. Accessed August 20, 2021.

CDC, 2021a, Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). February 17, 2021. https://www.cdc.gov/mis-c/hcp/.

CDC, 2021b, Health Equity Considerations and Racial and Ethnic Minority Groups. Updated April 19, 2021. https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/race-ethnicity.html. Accessed August 20, 2021. .

CDC, 2021c, COVID Data Tracker. Demographic trends of COVID-19 cases and deaths in the US reported to the CDC. www.cdc.gov/covid-data-tracker/index.html#demographics. Accessed August 2, 2021.

CDC, 2021d, COVID Data Tracker. Variant Proportions. https://covid.cdc.gov/covid-data-tracker/#variant-proportions . Accessed August 20, 2021.

CDC, 2021e, COVID-19 Vaccine Safety Update (slide presentation). https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/28-03-01/05-covid-Shimabukuro.pdf Accessed August 20, 2021.

CDC, 2021f, Update on Emerging SARS-CoV-2 Variants and COVID-19 vaccines (slide presentation). https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/04-COVID-Scobie-508.pdf. Accessed August 20, 2021.

CDC, 2021g, SARS-CoV-2 Variant Classifications and Definitions. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html. Accessed August 20, 2021.

CDC Advisory Committee on Immunization Practices, 2021a, COVID-19 VaST Work Group Report – May 17, 2021. https://www.cdc.gov/vaccines/acip/work-groups-vast/report-2021-05-17.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Facip%2Fwork-groups-vast%2Ftechnical-report-2021-05-17.html. Accessed August 20, 2021.

CDC Advisory Committee on Immunization Practices, 2021b, COVID-19 Vaccine Safety Technical (VaST) Work Group (slide presentation). April 23, 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-04-23/05-COVID-Lee-508.pdf Accessed August 20, 2021.

CDC Advisory Committee on Immunization Practices, 2021c, COVID-19 Vaccine Safety Technical (VaST) Work Group (slide presentation). June 23, 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/04-COVID-Lee-508.pdf. Accessed August 20, 2021.

FDA, 2020a, Emergency Use Authorization Review Memorandum for the Moderna COVID-19 Vaccine/mRNA-1273. December 18, 2020. https://www.fda.gov/media/144673/download.

FDA, 2020b, Emergency Use Authorization Review Memorandum for the Pfizer-BioNTech COVID-19 Vaccine/ BNT162b2. December 11, 2020. https://www.fda.gov/media/144416/download.

FDA, 2020c, Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020. https://www.fda.gov/media/139638/download.

FDA, 2021a, Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19. February 2021. https://www.fda.gov/media/142749/download.

FDA, 2021b, Emergency Use Authorization Amendment Review Memorandum (for use of the Pfizer COVID-19 Vaccine in adolescents). https://fda.report/media/149528/nr_EUA+27034.132+Review+Memo+Pfizer-BioNTech+COVID-19+Vaccine_REVISED24May_final.pdf.

Holshue, ML, C DeBolt, S Lindquist, KH Lofy, J Wiesman, H Bruce, C Spitters, K Ericson, S Wilkerson, A Tural, G Diaz, A Cohn, L Fox, A Patel, SI Gerber, L Kim, S Tong, X Lu, S Lindstrom, MA Pallansch, WC Weldon, HM Biggs, TM Uyeki, and SK Pillai, 2020, First Case of 2019 Novel Coronavirus in the United States, New England Journal of Medicine, 382(10):929-936.

Pawlowski, C, P Lenehan, A Puranik, V Agarwal, A Venkatakrishnan, MJM Niesen, JC O'Horo, A Virk, MD Swift, AD Badley, J Halamka, and V Soundararajan, 2021, FDA-authorized COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system, medRxiv:2021.2002.2015.21251623.

Thompson, MG, JL Burgess, AL Naleway, HL Tyner, SK Yoon, J Meece, LEW Olsho, AJ Caban-Martinez, A Fowlkes, K Lutrick, JL Kuntz, K Dunnigan, MJ Odean, KT Hegmann, E Stefanski, LJ Edwards, N Schaefer-Solle, L Grant, K Ellingson, HC Groom, T Zunie, MS Thiese, L Ivacic, MG Wesley, JM Lamberte, X Sun, ME Smith, AL Phillips, KD Groover, YM Yoo, J Gerald, RT Brown, MK Herring, G Joseph, S Beitel, TC Morrill, J Mak, P Rivers, KM Harris, DR Hunt, ML Arvay, P Kutty, AM Fry, and M Gaglani, 2021, Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March 2021, MMWR Morb Mortal Wkly Rep, 70(13):495-500.

World Health Organization, 2021a, WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int. Accessed August 20, 2021.

World Health Organization, 2021b, Weekly epidemiological update on COVID-19 - 1 June 2021. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---1-june-2021. Accessed August 20, 2021.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study C4591001

NCT04368728

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

Reviewer Comment: The protocol for this ongoing study has been amended over time to add study populations, interventions, and analyses not included in the original design and not pertinent to this BLA. The study design as described herein reflects objectives, endpoints, and monitoring pertaining to safety, immunogenicity, and efficacy evaluations following a 2-dose BNT162b2 primary series, according to protocol amendment 14, which was the active version at the time of the March 13, 2021 data cutoff. Secondary/exploratory objectives pertaining to immunobridging evaluations in individuals 12-15 years of age, re-vaccination (e.g., 3rd BNT162b2 dose), and evaluation of modified BNT162b2 vaccine formulations were beyond the scope of this BLA, and therefore not presented in this clinical review. Secondary objectives and associated efficacy analyses starting from 14 days after Dose 2, based on CDC definitions, were reviewed but not considered by the clinical reviewers as critically important to the interpretation of the primary endpoint. Lastly, the BLA submission did not include data to address asymptomatic COVID-19 infection, based on seroconversion or surveillance PCR testing or immunogenicity data from Phase 2/3; thus, study

objectives pertaining to asymptomatic infection and Phase 2/3 immunogenicity evaluations are not presented.

6.1.1 Objectives and Endpoints

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 incidence per 1000 person-years of follow-up based on laboratory-confirmed 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 incidence per 1000 person-years of follow-up based on laboratory-confirmed NAAT

Primary safety objective: To characterize the safety of BNT162b2.

Endpoints: solicited local adverse reactions (injection site pain, redness, swelling), solicited systemic adverse events (AE) (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), AEs, serious adverse events (SAEs)

Solicited AEs were assessed for the first 360 participants (Phase 2) and then a subset of at least 6,000 participants in Phase 2/3.

Pertinent secondary efficacy objectives

- To evaluate the efficacy of BNT162b2 against severe COVID-19 occurring from 7 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 for both populations: Severe COVID-19 incidence per 1000 person-years of follow-up

For all of the study objectives described above, NAAT could be confirmed in a central or local laboratory, unless otherwise specified. Evidence of past SARS-CoV-2 infection (before Dose 1) was documented serologically or virologically.

6.1.2 Design Overview

Study C4591001 is an ongoing, randomized Phase 1/2/3 study being conducted in the US, Argentina, Brazil, Germany, South Africa and Turkey. Initially, the study was

designed as a placebo-controlled Phase 1 study in healthy US adults to assess the safety and immunogenicity of several vaccine candidates and dose levels. In Phase 1, to facilitate review of phase 1 data in real time, the Applicant was not blinded to the vaccine assignment. The protocol was amended to include observer-blinded, placebo-controlled Phase 2 (US) and Phase 3 (international) portions to evaluate safety and clinical disease efficacy endpoints, initially in adults 18 years of age and older but later amended to include adolescents 16-17 years of age and then adolescents 12-15 years of age. Following FDA issuance of an EUA for BNT162b2, progressive unblinding to the randomized assignment began for all participants. This review focuses on the population of participants 16 years of age and older, the population proposed for initial licensure.

In Phase 1, two vaccine candidates were evaluated in adults who were not at high risk of SARS-CoV-2 exposure, without medical conditions that represented risk factors for more severe COVID-19, and without serologic/virologic evidence of SARS-CoV-2 infection. For each vaccine candidate, several dose levels were evaluated in adults 18 through 55 years of age, with progression to the next higher dose level and to adults 65 through 85 years of age based on recommendation from an Internal Review Committee (IRC). 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 selection of the final vaccine candidate and dose level (BNT162b2 30 µg) to proceed into Phase 2/3. Immune responses in Phase 1 (SARS-CoV-2 neutralizing titer, S1- and receptor binding domain- IgG) were assessed pre-Dose 1, after Dose 1 (at Days 7 and 21) and after Dose 2 (at 7 and 14 days and 1 and 6 months).

In Phase 2/3, enrolled participants were initially stratified by age (18-55 years and >55 years), with a goal of 40% enrollment in the older adults (>55 years of age). The protocol was later amended to include adolescents 16-17 years of age (and subsequently 12 to 15 years of age), following IRC review of safety data in adults; hence, the age strata for the initial EUA submission and for this BLA submission were revised as follows: 16-55 years of age, and >55 years of age. The study population for Phase 2/3 included 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, 3 weeks apart. The Phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 participants, and these participants also contribute to the overall efficacy and safety data in the Phase 3 portion.

Changes in the conduct of the study or planned analyses relevant to the proposed indication and use:

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

Other protocol amendments:

- Amendment 6, dated September 8, 2020: Added an exploratory objective to describe safety, immunogenicity, and efficacy in participants with stable HIV disease; increased the sample size for Phase 2/3 to ~44,000.
- Amendment 8, dated October 15, 2020: Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs.
- Amendment 12, dated January 14, 2021: participants ≥16 years of age who originally received placebo would be eligible for receipt of BNT162b2, in a phased manner.

Per protocol, since December 14, 2020, following issuance of the Emergency Use Authorization for the Pfizer-BioNTech COVID-19 Vaccine, Phase 2/3 participants ≥16 years of age in the vaccine and placebo groups were progressively unblinded to their treatment assignment (when eligible per local recommendations). Participants initially randomized to the placebo group were offered BNT162b2 vaccination at a time no later than the 6-month follow-up visit after the second placebo vaccination. For participants unblinded to his/her vaccine assignment, follow-up evaluations thereafter were conducted in an open-label manner.

> *Reviewer Comment:* During the blinded placebo-controlled time period in Phases 2 and 3, study staff who prepared and administered the study interventions were unblinded to the treatment assignment, due to differences in appearance of BNT162b2 and saline placebo, and study investigators/personnel collecting and evaluating safety and efficacy information were blinded to the participants' treatment assignment (observer-blinded). In the package insert, double-blind refers only to the study investigators/personnel collecting and evaluating safety and efficacy information and the participant.
>
> After BNT162b2 became available for emergency use, participants who elected to receive BNT162b2 were unblinded to their initial study intervention assignment. The Applicant and site personnel who are responsible for the ongoing conduct of the study remain blinded to the data from participants whose treatment assignment has not been disclosed.

6.1.3 Population

Phase 1: key eligibility criteria described in Section 6.1.2 Design Overview.

Phase 2/3
Key inclusion criteria

- Healthy or had pre-existing stable chronic medical conditions
- ≥12 years of age. Individuals <18 years of age were not enrolled in the EU.
- At higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, frontline essential workers).

Key exclusion criteria
Phase 2 only: Known infection with HIV, hepatitis C virus, or hepatitis B virus

- Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19

- Known or suspected immunodeficiency, or received/planning treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt throughout the study
- Women who are pregnant or breastfeeding
- Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Criteria for temporarily delaying enrollment/randomization/study intervention administration

- Current febrile illness (T ≥38°C) or other acute illness within 48 hours before study intervention administration, including symptoms that could represent a potential COVID-19 illness: new or increased cough; new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste/smell, sore throat, diarrhea, vomiting.
- Receipt or planning to receive a seasonal or pandemic influenza vaccine within 14 days, or any other non-study vaccine within 28 days, before study vaccination.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The BNT162b2 (30 µg) vaccine candidate was selected for further evaluation in Phase 2/3. BNT162b2 contains a nucleoside-modified messenger RNA that encodes the viral spike (S) glycoprotein of SARS-CoV-2 encapsulated in a lipid nanoparticle. Each dose also includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

6.1.5 Directions for Use

Two doses of BNT162b2 (0.3 mL per dose) were administered 3 weeks apart. Each dose was injected intramuscularly into the deltoid muscle.

See the full prescribing information for further information regarding preparation of BNT162b2.

6.1.6 Sites and Centers

A total of 153 clinical sites enrolled participants for Study C4591001 [US (131), Turkey (9), Germany (6), South Africa, (4), Brazil (2) and Argentina (1)].

6.1.7 Surveillance/Monitoring

Efficacy

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 nucleic acid amplification-based test (NAAT), to detect SARS-CoV-2. Case ascertainment is based on central laboratory NAAT results, 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 primary and secondary efficacy endpoints were analyzed in the protocol-specified event-driven final efficacy analysis after at least 164 COVID-19 cases were accrued (see Section 6.1.9). Participants are expected to participate for a maximum of approximately 26 months.

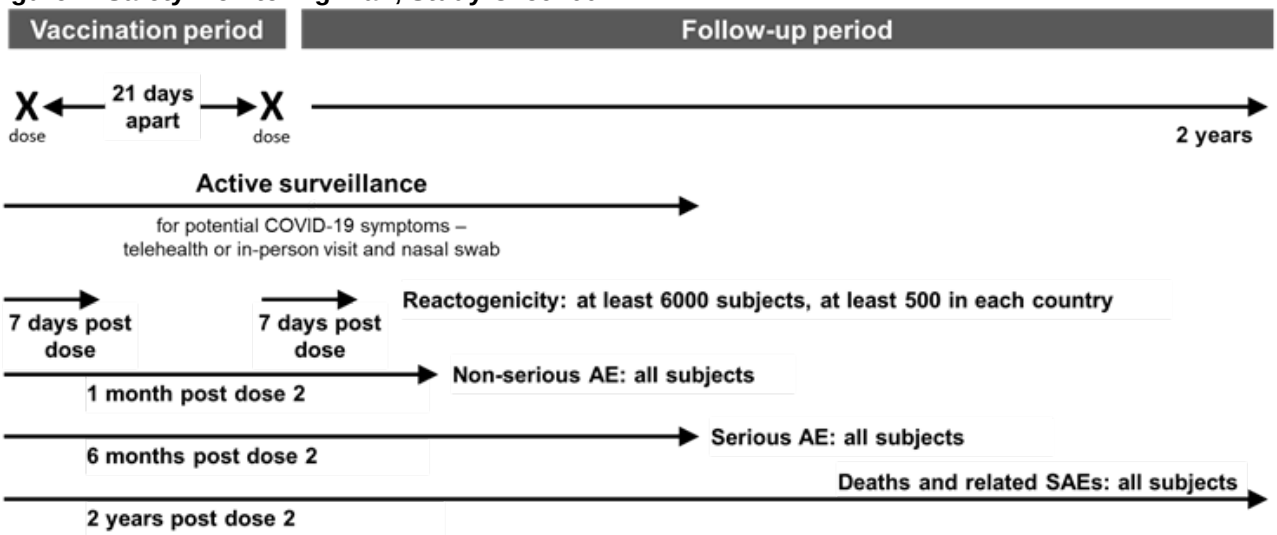
Safety

Solicited AEs (local and systemic reactions, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose) were assessed for the first 360 Phase 2 participants and then a subset of at least 6,000 participants in Phase 2/3.

> *Reviewer Comment:* The total number of participants enrolled in the reactogenicity subset was 9,839.

The subset of Phase 2/3 participants ≥16 years of age with stable HIV were analyzed separately per protocol. For all participants, all unsolicited adverse events (AEs) were collected from Dose 1 to 1 month after the last dose and all serious AEs (SAEs) from Dose 1 to 6 months after the last dose. The planned safety follow-up for currently enrolled adolescents and adults is a maximum of 26 months (i.e., through 24 months after vaccination #2) and will include collection of deaths and related SAEs reported after 6 months post-Dose 2. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study C4591001



Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), and antipyretic/pain medication use were recorded in an e-diary. For Phase 3 participants who were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as unsolicited AEs.

Clinical laboratory tests were assessed routinely in Phase 1 only, at 1-week post-vaccination.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. These illnesses were evaluated and reported as SAEs.

In Phase 2/3, monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule for the theoretical concern of vaccine-enhanced disease was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants, and alert criteria were triggered when this probability was less than 11%. Participants who discontinued study intervention continued the protocol-specified follow-up procedures.

After BNT162b2 was granted emergency use authorization (December 11, 2020), unblinding procedures were initiated to vaccinate the placebo group. Please see Section 6.1.10.1 (Population enrolled/analyzed) for additional details.

6.1.8 Endpoints and Criteria for Study Success

Efficacy Evaluation
The case definition for a confirmed case of COVID-19 for the primary efficacy endpoint, was the presence of at least one of the following symptoms and a positive SARS-CoV-2 NAAT within 4 days of the symptomatic period:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrhea
- Vomiting

The case definition for severe COVID-19 case included a confirmed COVID-19 case with at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2≤93% on room air at sea level, or PaO2/FiO_2<300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation)
- 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

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Study success criteria: In Phase 2/3, the assessment of VE was based on posterior probability of VE_1>30% and VE_2>30%, where VE_1 represented VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represented 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 were based on the posterior probability, i.e. Pr(VE >30%|data) at the current number of cases. Efficacy was declared if the posterior probability was 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 was met, the second primary objective was evaluated at the final analysis.

Pertinent secondary efficacy endpoint

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either ≥7 days after Dose 2

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 participants 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 (IAs) 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 $\theta = r(1-VE)/(1+r(1-VE))$, 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 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. Secondary endpoints were evaluated similarly to the primary endpoints.

After the protocol-specified event-driven final efficacy analyses at 170 cases, updated efficacy analyses on primary and secondary efficacy endpoints were performed with additional data accrued during the blinded placebo-controlled follow-up time period. 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, r(VE >30%|data), was also provided.

> *Reviewer Comment:* Although the total planned follow-up for study participants is 2 years, due to complexities introduced by unblinding and placebo cross-over following emergency use authorization of the vaccine longer term vaccine effectiveness (beyond the evaluable period from placebo-controlled follow-up in the clinical trial) will be best evaluated in observational studies.

Solicited safety analyses were based on participants in the reactogenicity subset who received at least one dose of the vaccine and responded yes or no to any reaction within 7 days of each dose. Unsolicited safety analyses were based on the safety population, which consisted of participants randomized in the Phase 2/3 study who received at least one dose of the vaccine, analyzed according to the vaccine received. Safety endpoints were summarized descriptively for the number of participants within the analysis set reporting at least one event in each category.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The study protocol was revised to allow participants ≥16 years of age who originally received placebo the opportunity to receive BNT162b2 following local or national recommendations or following completion of the active safety surveillance period, following issuance of the EUA (protocol amendment 10). On December 14, 2020, the process of disclosing vaccine assignments for all trial participants ≥16 years of age began (following issuance of the EUA for use of the Pfizer-BioNTech COVID-19 vaccine in individuals 16 years of age and older). Hence, for each trial participant, there are 2 periods in the study: enrollment into the observer-blind phase until the date of vaccine disclosure and the time in the study after disclosure. Participants who originally were randomized to BNT162b2 are continuing to be followed for safety as specified in the protocol. The safety data for participants who originally were randomized to and received placebo prior to disclosure of vaccine assignment include blinded data that contribute to controlled assessment of safety compared to individuals who randomly assigned to BNT162b2. After vaccine treatment disclosure and the administration of BNT162b2, the placebo participants can no longer be used for direct comparison with those who originally were randomized to BNT162b2. Even though individuals were unblinded on different days after December 14, 2020, the difference in the total blinded follow-up duration is minor between the treatment arms. Thus, the analysis of the observer-blinded, placebo-controlled portion of the study as well as the open-label

portion is reported in frequencies, such that the number of participants within the analysis set reporting at least one event in each category is displayed.

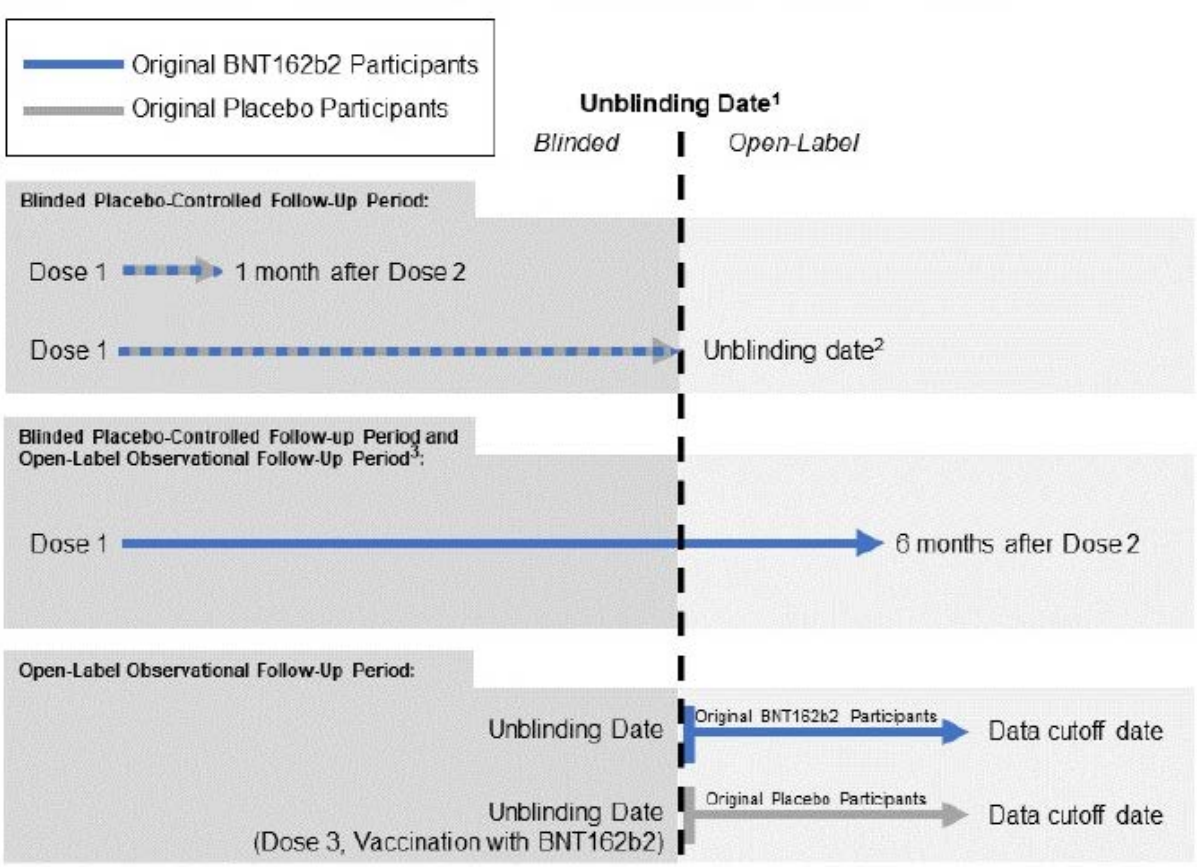
Safety data presented for Phase 3 of Study C4591001, based on the data cutoff date of March 13, 2021, include:

1. Blinded placebo-controlled period: Dose 1 to 1 month after Dose 2 and to unblinding date:
   - Participants with up to ~6 months after Dose 2 (N=43,847; BNT162b2 group N=21,926 and placebo group N=21,921).
   - Solicited local ARs and systemic AEs were assessed during this time period from a subset of participants.
2. Open-label observational period: from time of unblinding to data cutoff date:
   - Participants originally randomized to BNT162b2 (N=20,309)
   - Participants originally randomized to placebo who then received BNT162b2 (N=19,525)
   - Participants originally randomized to placebo who had confirmed COVID-19 then received BNT162b2 (N=852)
   - Only unsolicited AEs (AEs, SAEs and adverse events of special interest [AESIs]) were assessed during this time period.
3. Cumulative follow-up from Dose 1 to at least 6 months after Dose 2:
   - Participants originally randomized to BNT162b2 (inclusive of blinded data and open-label data through the March 13, 2021 data cutoff). (Total N=12,006: 16-55 years of age/younger age group [N =6,666] and >55 years of age/older age group [N =5,340]).

   Reviewer Comment: The BLA safety database exceeded FDA expectations for at least 3,000 vaccine recipients in each age group with at least 6 months of total safety follow-up.

A graphic of these three different time periods taken into consideration for the evaluation of the safety data is displayed in Figure 2, below.

Figure 2. Phase 2/3 Safety Analyses: Time Period and Analysis Groups



Source: STN 125742.0 c4591001-interim-mth6-report-body.pdf. Figure 11 (p 140).
[1] Will vary by participant. Adverse event data analyzed from Dose 1 to unblinding date, or from unblinding date to data cutoff date.
[2] Up to ~6 months after Dose 2.
[3] Cumulative BNT162b2 follow-up to at least 6 months after Dose 2.

Analysis populations

Population	Description
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 dose of vaccine. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.
Reactogenicity subset	Subset of participants in the safety population who had e-diary data reported after vaccination.

Data analysis cutoff dates:

- August 24, 2020 (Phase 1 safety and immunogenicity data through 1 month after Dose 2)
- September 2, 2020 (Phase 2 safety data through 7 days after Dose 2)
- November 4, 2020 (Phase 2/3 first interim analysis for efficacy)

- November 14, 2020 (Phase 2/3 final analysis for efficacy, safety data for 37,586 participants with a median follow-up of at least 2 months, and available safety data for all 43,252 participants)
- March 13, 2021 (Phase 2/3 updated vaccine efficacy analysis and safety follow-up)

6.1.10.2 Demographics

A total of 42,436 randomized participants 16 years of age and older (21,136 in the BNT162b2 group and 21,300 in the placebo group) comprise the evaluable efficacy population from the March 13, 2021 data cutoff. Overall, the evaluable efficacy population included 49.2% females; 82.0% White, 9.5% African American, 4.4% Asian, and <4% from other racial groups; 25.5% of participants were Hispanic/Latino; 20.8% of participants were ≥65 years of age. The median age was 51 years. One or more comorbidities that increase the risk of severe COVID-19 disease were present among 45.8% of participants. The most frequently reported comorbidity was obesity (34.5%). Only 3.1% of participants had evidence of prior SARS-CoV-2 infection. Geographically, 76.4% of participants lived in the US, 12.7% lived in Argentina, 6.8% lived in Brazil, and <2% of participants lived in each of the following countries: Germany, Turkey and South Africa. The demographics were balanced between the treatment groups. The demographics of the evaluable efficacy population used for the updated vaccine efficacy analysis of the second primary endpoint (participants with or without evidence of SARS-CoV-2 infection prior to 7 days post-Dose 2) is displayed in Table 6.

Table 6. 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

	Vaccine Group (as Randomized)		
Characteristic	**BNT162b2 (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 (15.99)	49.7 (16.03)	49.7 (16.01)
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: 16-18 years	370 (1.8)	362 (1.7)	732 (1.7)
Age Group: 18-55 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)

Characteristic	Vaccine Group (as Randomized)		
	BNT162b2 (N[a] =21136) n[b] (%)	**Placebo (N[a] =21300) n[b] (%)**	**Total (N[a] =42436) n[b] (%)**
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)
Country: United States	16141 (76.4)	16285 (76.5)	32426 (76.4)

Source: STN 125742.032 c4591001-508-efficacy tables, Table F, Page 9
Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: HIV-positive participants are included in this summary but not included in the analyses of the overall study objectives.
[a.] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b.] n = Number of participants with the specified characteristic.
[c.] Participants who had BMI ≥30 kg/m2.
[d.] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index category or BMI ≥30 kg/m2.
[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.

The population for the updated vaccine efficacy analysis of the first primary endpoint included 40,111 participants 16 years of age and older (19,993 in the BNT162b2 group and 20,118 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose and who were HIV negative. Demographics for this analysis population were not meaningfully different from those in the table above, with the exception of being limited to participants without evidence of SARS-CoV-2 infection prior to 7 days post-Dose 2.

The safety population included 44,047 participants 16 years of age and older (22,026 in the BNT162b2 group and 22,021 in the placebo group). Overall, the safety population included 49.1% females; 82.0% White, 9.6% African American, 4.3% Asian, and <2% from other racial groups; 25.9% of participants were Hispanic/Latino; 20.7% of participants were ≥65 years of age. The median age was 51 years. One or more comorbidities that increase the risk of severe COVID-19 disease were present among 45.8% of participants. Only 3.2% of participants had evidence of prior SARS-CoV-2 infection. Geographically, 76.3% of participants lived in the US, 13.1% lived in Argentina, 6.6% lived in Brazil and, <2% of participants lived in each of the following countries: Germany, Turkey and South Africa. The demographics were balanced between the treatment groups. Table 7 presents the specific demographic characteristics in the studied population.

Table 7. Demographics and Other Baseline Characteristics, Participants 16 Years of Age and Older, Safety Population

	Vaccine Group (as Administered)		
Characteristic	**BNT162b2 (N[a] =22026) n[b] (%)**	**Placebo (N[a] =22021) n[b] (%)**	**Total (N[a] =44047) n[b] (%)**
Sex: Female	10704 (48.6)	10923 (49.6)	21627 (49.1)
Sex: Male	11322 (51.4)	11098 (50.4)	22420 (50.9)
Age at Vaccination: Mean years (SD)	49.7 (15.99)	49.6 (16.05)	49.7 (16.02)
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: 16-17 years	378 (1.7)	376 (1.7)	754 (1.7)
Age Group: 18-55 years	12691 (57.6)	12719 (57.8)	25410 (57.7)
Age Group: >55 years	8957 (40.7)	8926 (40.5)	17883 (40.6)
Age Group: ≥65 years	4552 (20.7)	4545 (20.6)	9097 (20.7)
Race: American Indian or Alaska Native	221 (1.0)	217 (1.0)	438 (1.0)
Race: Asian	952 (4.3)	942 (4.3)	1894 (4.3)
Race: Black or African American	2098 (9.5)	2118 (9.6)	4216 (9.6)
Race: Native Hawaiian or Other Pacific Islander	58 (0.3)	32 (0.1)	90 (0.2)
Race: White	18056 (82.0)	18064 (82.0)	36120 (82.0)
Race: Multiracial	550 (2.5)	533 (2.4)	1083 (2.5)
Race: Not reported	91 (0.4)	115 (0.5)	206 (0.5)
Ethnicity: Hispanic or Latino	5704 (25.9)	5695 (25.9)	11399 (25.9)
Ethnicity: Not Hispanic or Latino	16211 (73.6)	16212 (73.6)	32423 (73.6)
Ethnicity: Not reported	111 (0.5)	114 (0.5)	225 (0.5)
Obesity: Yes[c]	7543 (34.2)	7629 (34.6)	15172 (34.4)
Obesity: No	14483 (65.8)	14392 (65.4)	28875 (65.6)
Comorbidities: Yes[d]	10119 (45.9)	10071 (45.7)	20190 (45.8)
Comorbidities: No	11907 (54.1)	11950 (54.3)	23857 (54.2)
Baseline evidence of prior SARS-CoV-2 infection: Negative[f]	21185 (96.2)	21180 (96.2)	42365 (96.2)
Baseline evidence of prior SARS-CoV-2 infection: Positive[e]	689 (3.1)	716 (3.3)	1405 (3.2)
Baseline evidence of prior SARS-CoV-2 infection: Missing	152 (0.7)	125 (0.6)	277 (0.6)
Country: Argentina	2883 (13.1)	2881 (13.1)	5764 (13.1)
Country: Brazil	1452 (6.6)	1448 (6.6)	2900 (6.6)
Country: Germany	249 (1.1)	250 (1.1)	499 (1.1)
Country: South Africa	401 (1.8)	399 (1.8)	800 (1.8)
Country: Turkey	249 (1.1)	249 (1.1)	498 (1.1)
Country: United States	16792 (76.2)	16794 (76.3)	33586 (76.3)

Source: STN 125742.037 c4591001-508-safety tables, Table E, Page 9
Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: HIV-positive participants are included in this summary but not included in the analyses of the overall study objectives.
[a.] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b.] n = Number of participants with the specified characteristic.
[c.] Participants who had BMI ≥30 kg/m2.
[d.] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index category (see Appendix A) or BMI ≥30 kg/m2.
[e.] Positive N-binding ant body 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.

The demographics tables above include participants with chronic, stable HIV infection, but they are excluded from the analysis populations for the efficacy and safety results in

Sections 6.1.11 and 6.1.12. Efficacy was not evaluated in participants with chronic, stable HIV infection. The safety analyses for this population are discussed in Section 9.1.6.

6.1.10.3 Subject Disposition

The overall study disposition tables are presented below in Table 8 (Blinded Follow-up Time Period) and Table 9 (Open-label Unblinded Follow-up Time Period). Overall, few participants were discontinued or lost to follow-up and these discontinuations were generally balanced between treatment groups.

A total of 87 (0.4%) Phase 2/3 original BNT162b2 participants received Dose 1 of BNT162b2 during the blinded placebo-controlled follow-up period and then received Dose 2 of BNT162b2 during the open-label follow-up period (when they were unblinded).

During the open-label follow-up period, most participants originally randomized to the placebo group for Doses 1 and 2 of study vaccine received BNT162b2 as Doses 3 and 4 (88.8% and 72.4%, respectively) of study vaccine. Most participants who received Dose 3 but not Dose 4 were within the 3-week window between the two doses as of the data cutoff date. There were few participants in this group (0.1%) who were withdrawn from the study, and most were due to withdrawals by the participant. The number of participants originally randomized to the placebo group who were unblinded and received BNT162b2 was 19,525. Additionally, 839 of the initial randomized placebo recipients (610 in the younger age group and 229 in the older age group) either opted not to receive vaccine after unblinding or had not had the opportunity to receive BNT162b2 at the time of the March 13, 2021 data cutoff.

Table 8. Study Disposition, Phase 2/3 Participants 16 Years of Age and Older, Blinded Follow-up Period

	Vaccine Group (as Randomized)		
Disposition	**BNT162b2 (N[a]=22085) n[b] (%)**	**Placebo (N[a]=22080) n[b] (%)**	**Total (N[a]=44165) n[b] (%)**
Randomized	22085 (100.0)	22080 (100.0)	44165 (100.0)
Not vaccinated	55 (0.2)	50 (0.2)	105 (0.2)
Original blinded placebo-controlled follow-up period			
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)
Discontinued from original blinded placebo-controlled vaccination period[c]	352 (1.6)	528 (2.4)	880 (2.0)
Reason for discontinuation			
Lost to follow-up	151 (0.7)	153 (0.7)	304 (0.7)
Withdrawal by subject	109 (0.5)	181 (0.8)	290 (0.7)
No longer meets eligibility criteria	26 (0.1)	120 (0.5)	146 (0.3)
Adverse event	27 (0.1)	26 (0.1)	53 (0.1)
Physician decision	5 (0.0)	8 (0.0)	13 (0.0)
Pregnancy	6 (0.0)	6 (0.0)	12 (0.0)
Protocol deviation	3 (0.0)	8 (0.0)	11 (0.0)
Death	3 (0.0)	4 (0.0)	7 (0.0)
Medication error without associated AE	3 (0.0)	2 (0.0)	5 (0.0)
Withdrawal by parent/guardian	1 (0.0)	0	1 (0.0)

	Vaccine Group (as Randomized)		
Disposition	**BNT162b2 (N[a]=22085) n[b] (%)**	**Placebo (N[a]=22080) n[b] (%)**	**Total (N[a]=44165) n[b] (%)**
Other	18 (0.1)	20 (0.1)	38 (0.1)
Unblinded before 1-month post–Dose 2 visit	253 (1.1)	240 (1.1)	493 (1.1)
Completed 1-month post–Dose 2 visit	21382 (96.8)	21293 (96.4)	42675 (96.6)
Withdrawn from the study	343 (1.6)	484 (2.2)	827 (1.9)
Withdrawn after Dose 1 and before Dose 2	176 (0.8)	211 (1.0)	387 (0.9)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	100 (0.5)	139 (0.6)	239 (0.5)
Withdrawn after 1-month post–Dose 2 visit	67 (0.3)	134 (0.6)	201 (0.5)
Reason for withdrawal from the study			
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 (0.0)	24 (0.1)	35 (0.1)
Death	16 (0.1)	15 (0.1)	31 (0.1)
Adverse event	9 (0.0)	8 (0.0)	17 (0.0)
Physician decision	3 (0.0)	6 (0.0)	9 (0.0)
No longer meets eligibility criteria	1 (0.0)	4 (0.0)	5 (0.0)
Pregnancy	0	1 (0.0)	1 (0.0)
Medication error without associated AE	1 (0.0)	0	1 (0.0)
Withdrawal by parent/guardian	1 (0.0)	0	1 (0.0)
Other	5 (0.0)	9 (0.0)	14 (0.0)

Source: STN 125742.037 c4591001-508-safety tables, Table B, Page 1
Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but analyzed and reported separately.
Note: Participants randomized but did not sign informed consent or had a significant quality event due to lack of PI oversight are not included in any analysis population.
Note: Because of a dosing error, 4 participants received an additional dose of BNT162b2 at an unscheduled visit after receiving 1 dose of BNT162b2 and 1 dose of placebo.
[a.] N = number of randomized participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b.] n = Number of participants with the specified characteristic.
[c.] Original blinded placebo-controlled vaccination period is defined as the time period from Dose 1 to 1 month post–Dose 2.

Table 9. Study Disposition, Phase 2/3 Participants 16 Years of Age and Older, Open-label (Unblinded) Follow-up Period

	Vaccine Group (as Randomized)	
Disposition	**BNT162b2 (N[a] =22085) n[b] (%)**	**Placebo (N[a] =22080) n[b] (%)**
Randomized	22085 (100.0)	22080 (100.0)
Not vaccinated	55 (0.2)	50 (0.2)
Originally randomized to BNT162b2	20404 (92.4)	
Received Dose 2/unplanned dose	87 (0.4)	
Completed 6-month post–Dose 2 visit	6414 (29.0)	
Withdrawn from the study	105 (0.5)	
Withdrawn before 6-month post–Dose 2 visit	103 (0.5)	
Withdrawn after 6-month post–Dose 2 visit	2 (0.0)	
Reason for withdrawal from the study		
Withdrawal by subject	56 (0.3)	
Protocol deviation	35 (0.2)	
Lost to follow-up	4 (0.0)	
Death	3 (0.0)	
Physician decision	2 (0.0)	
Adverse event	1 (0.0)	

	Vaccine Group (as Randomized)	
Disposition	**BNT162b2 (N[a] =22085) n[b] (%)**	**Placebo (N[a] =22080) n[b] (%)**
No longer meets eligibility criteria	1 (0.0)	
Other	3 (0.0)	
Originally randomized to placebo		20948 (94.9)
Completed 6-month post-Dose 2 visit		153 (0.7)
Withdrawn from the study after unblinding and before Dose 3		497 (2.3)
Received Dose 3 (first dose of BNT162b2)		19612 (88.8)
Received Dose 4 (second dose of BNT162b2)		15986 (72.4)
Discontinued from open-label vaccination period		24 (0.1)
Reason for discontinuation from open-label vaccination period		
Protocol deviation		6 (0.0)
Adverse event		5 (0.0)
Withdrawal by subject		5 (0.0)
Pregnancy		4 (0.0)
Death		2 (0.0)
Lost to follow-up		2 (0.0)
Completed 1-month post-Dose 4 visit		7209 (32.6)
Withdrawn from the study		14 (0.1)
Withdrawn after Dose 3 and before Dose 4		11 (0.0)
Withdrawn after Dose 4 and before 1-month post-Dose 4 visit		2 (0.0)
Withdrawn after 1-month post-Dose 4 visit		1 (0.0)
Reason for withdrawal from the study		
Withdrawal by subject		7 (0.0)
Protocol deviation		3 (0.0)
Death		2 (0.0)
Adverse event		1 (0.0)
Lost to follow-up		1 (0.0)

Source: STN 125742.037 c4591001-508-safety tables Table B, Page 1
Note: Open-label (unblinded) vaccination period is defined as the time period from Dose 3 (first dose of BNT162b2) to 1 month post–Dose 4 (second dose of BNT162b2).
Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but analyzed and reported separately.
Note: Participants randomized but did not sign informed consent or had a significant quality event due to lack of PI oversight are not included in any analysis population.
[a.] N = number of randomized participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b.] n = Number of participants with the specified characteristic.

The duration of blinded follow-up after completion of the 2-dose vaccine series in the safety and evaluable efficacy populations are displayed in Table 10 and Table 11, respectively. Because this study is ongoing, and participants were unblinded to their study intervention following issuance of the EUA in December 2020 or at their 6-month follow-up visit, the number of participants with blinded follow-up decreases beyond 6 months, as expected.

Table 10. Blinded Follow-up Duration After Dose 2, Participants 16 Years of Age and Older, Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 N[a] =22026	Placebo N[a] =22021	Total N[a] =44047
Length of Follow-up[c]	n[b] (%)	n[b] (%)	n[b] (%)
<2 Months	1251 (5.7)	1331 (6.0)	2582 (5.9)
≥2 Month to <4 months	7744 (35.2)	8070 (36.6)	15814 (35.9)
≥4 Months to <6 months	11253 (51.1)	11316 (51.4)	22569 (51.2)
≥6 Months	1778 (8.1)	1304 (5.9)	3082 (7.0)

Source: STN 125742.0 c4591001-interim-mth6-report-body.pdf, Table 9, page 84
[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n = number of participants with the specified characteristic.
[c] Length of follow-up is the total exposure from Dose 2 to cutoff date or the date of unblinding, whichever date was earlier.

Table 11. Blinded Follow-up Duration after Dose 2, Phase 2/3 Participants 16 Years of Age and Older, Evaluable Efficacy Population

	Vaccine Group (as Randomized)		
	BNT162b2 N[a] =21047	Placebo N[a] =21210	Total N[a] =42257
Duration of Follow-up	n[b] (%)	n[b] (%)	n[b] (%)
<2 Months	840 (4.0)	910 (4.3)	1750 (4.1)
≥2 Months to <4 Months	7411 (35.2)	7851 (37.0)	15262 (36.1)
≥4 Months to <6 Months	11031 (52.4)	11158 (52.6)	22189 (52.5)
≥6 Months	1765 (8.4)	1291 (6.1)	3056 (7.2)

Source: Source: STN 125742.0.52 Table 1, page 4
Note: HIV-positive participants are not included in this summary because they are not included in the efficacy analyses.
[a.] N = number of participants in the analysis population for the primary efficacy endpoints (evaluable participants with and without evidence of prior infection). This value is the denominator for the percentage calculations
[b.] n = Number of participants with the specified characteristic.

The number of participants originally randomized to the BNT162b2 group who received both doses, were included in the evaluable efficacy population and had at least 6 months of blinded follow-up after Dose 2 is 1765 (8.4%).

Disposition tables are presented below in Table 12 (efficacy analysis populations) and Table 13 (Phase 2/3 safety population). Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups.

For the evaluable efficacy population, most participants who were excluded from the analysis had not received all vaccinations as randomized or did not receive Dose 2 within the predefined window (i.e., 19 to 42 days after Dose 1). A total of 240 participants in the BNT162b2 group and 60 participants in the placebo group were excluded for having important protocol deviations (PDs) on or prior to 7 days after Dose 2. In the BNT162b2 group, most of these deviations were related to improper administration of the investigational product (203 participants, as compared with 23 participants in the placebo group). Specifically, in the BNT162b2 group most PDs were due to dosing/administration errors (errors in dilution of the vaccine, 76 participants) or administration of investigational product that was deemed not suitable for use (temperature excursions in shipment or storage at the distributor, 110 participants) that would have not applied to placebo.

Table 12. Disposition, Participants 16 Years of Age and Older, Efficacy Population

	Vaccine Group (as Randomized)		
Disposition	**BNT162b2 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)
Participants without evidence of infection before Dose 1	21172 (95.9)	21168 (95.9)	42340 (95.9)
Participants 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)
Dose 2 all-available efficacy population	21648 (98.0)	21624 (97.9)	43272 (98.0)
Participants without evidence of infection prior to 7 days after Dose 2	20536 (93.0)	20487 (92.8)	41023 (92.9)
Participants 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)
Participants without evidence of infection prior to 7 days after Dose 2	20064 (90.8)	20197 (91.5)	40261 (91.2)
Participants 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)

Source: STN 125742.032 c4591001-508-efficacy tables, Table D, Page 7
Note: HIV-positive participants are included in this summary but not included in the analyses of the overall study objectives.
[a.] n = Number of participants with the specified characteristic.
[b.] These values are the denominators for the percentage calculations.
[c.] Participants may have been excluded for more than 1 reason.

The safety population included a total of 44,050 participants: 22,026 participants in the BNT162b2 group and 22,021 participants in the placebo group. Most of the 115 participants excluded from the safety population were excluded because they did not receive study vaccine.

Table 13. Disposition, Participants 16 Years of Age and Older, Safety Population

	Vaccine Group (as Administered)		
Disposition	**BNT162b2 (N[a] =22026) n[b] (%)**	**Placebo (N[a] =22021) n[b] (%)**	**Total (N[a] =44050) n[b] (%)**
Randomized			44165
Not vaccinated			105
Vaccinated	22026 (100.0)	22021 (100.0)	44050 (100.0)
Completed 1 dose	22026 (100.0)	22021 (100.0)	44050 (100.0)
Completed 2 doses	21674 (98.4)	21645 (98.3)	43319 (98.3)
Safety population	22026 (100.0)	22021 (100.0)	44050 (100.0)
Reactogenicity subset	5033 (22.9)	5032 (22.9)	10068 (22.9)
HIV-positive	100 (0.5)	100 (0.5)	200 (0.5)
Indeterminate vaccine			3 (0.0)
Participants excluded from safety population			115 (0.3)
Reason for exclusion			
Participant did not receive study vaccine			105 (0.2)
Unreliable data due to lack of PI oversight			10 (0.0)
Completed at least 6 months follow-up after Dose 2 in blinded placebo-controlled follow-up period	1778 (8.1)	1304 (5.9)	3082 (7.0)
Completed at least 6 months follow-up after Dose 2 in blinded and open-label follow-up period	12006 (54.5)		
Completed 1-month post–Dose 2 visit (vaccination period)	21378 (97.1)	21291 (96.7)	42669 (96.9)
Discontinued from vaccination period but continued in the study up to 1-month post–Dose 2 visit	350 (1.6)	520 (2.4)	873 (2.0)
Discontinued after Dose 1 and before Dose 2	233 (1.1)	359 (1.6)	595 (1.4)
Discontinued after Dose 2 and before 1-month post–Dose 2 visit	117 (0.5)	161 (0.7)	278 (0.6)
Reason for discontinuation from vaccination period			
Lost to follow-up	151 (0.7)	149 (0.7)	300 (0.7)
Withdrawal by subject	108 (0.5)	181 (0.8)	289 (0.7)
No longer meets eligibility criteria	25 (0.1)	120 (0.5)	145 (0.3)
Adverse event	27 (0.1)	26 (0.1)	53 (0.1)
Physician decision	5 (0.0)	7 (0.0)	12 (0.0)
Pregnancy	6 (0.0)	6 (0.0)	12 (0.0)
Protocol deviation	3 (0.0)	8 (0.0)	11 (0.0)
Death	3 (0.0)	4 (0.0)	7 (0.0)
Medication error without associated adverse event	2 (0.0)	0	5 (0.0)
Withdrawal by parent/guardian	1 (0.0)	0	1 (0.0)
Other	19 (0.1)	19 (0.1)	38 (0.1)
Withdrawn from study before 1-month post–Dose 2 visit	273 (1.2)	344 (1.6)	617 (1.4)
Withdrawn after Dose 1 and before Dose 2	173 (0.8)	205 (0.9)	378 (0.9)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	100 (0.5)	139 (0.6)	239 (0.5)
Reason for withdrawal			

	Vaccine Group (as Administered)		
Disposition	**BNT162b2 (N[a] =22026) n[b] (%)**	**Placebo (N[a] =22021) n[b] (%)**	**Total (N[a] =44050) n[b] (%)**
Lost to follow-up	151 (0.7)	153 (0.7)	304 (0.7)
Withdrawal by subject	101 (0.5)	168 (0.8)	269 (0.6)
Adverse event	9 (0.0)	7 (0.0)	16 (0.0)
Physician decision	3 (0.0)	5 (0.0)	8 (0.0)
Death	3 (0.0)	4 (0.0)	7 (0.0)
Protocol deviation	0	1 (0.0)	1 (0.0)
Medication error without associated adverse event	1 (0.0)	0	1 (0.0)
No longer meets eligibility criteria	0	1 (0.0)	1 (0.0)
Withdrawal by parent/guardian	1 (0.0)	0	1 (0.0)
Other	4 (0.0)	5 (0.0)	9 (0.0)

Source: STN 125742.037 c4591001-508-safety tables, Table C, Page 6
Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but not included in the analyses of the overall study objectives.
Note: Participants randomized but did not sign informed consent or had a significant quality event due to lack of PI oversight are not included in any analysis population.
Note: Because of a dosing error, Participants C4591001 (b) (6) , C4591001 (b) (6) , C4591001 (b) (6) and C4591001 (b) (6) received an additional dose of BNT162b2 (30 µg) at an unscheduled visit after receiving 1 dose of BNT162b2 (30 µg) and 1 dose of placebo.
Note: "Indeterminate vaccine" refers to participants whose vaccine group (as administered) could not be determined. These participants were included in the number of participants for "Total" column. These participants were not included in the safety analysis but their safety data are listed separately.
[a.] N = number of randomized participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b.] n = Number of participants with the specified characteristic

The disposition tables above include participants with chronic, stable HIV infection, but they are excluded from the analysis populations for the efficacy and safety results in Sections 6.1.11 and 6.1.12. Efficacy was not evaluated in participants with chronic, stable HIV infection. The safety analyses for this population are discussed in Section 9.1.6.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Vaccine Efficacy (Evaluable Efficacy Population)

Protocol-specified, event-driven final primary efficacy analysis
For the primary efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2. The population in the protocol-specified, event-driven final primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020 and followed for the development of COVID-19 through November 14, 2020.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0% (95% credible interval: 90.0, 97.9), which met the pre-specified success criterion. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group. This protocol-specified, event-driven final primary efficacy

analysis was the basis for issuance of the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine on December 11, 2020. Please refer to the EUA Review Memo for the Pfizer COVID-19 Vaccine for additional details from that analysis time point.

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. All of the following updated primary and secondary VE analyses are from this blinded placebo-controlled follow-up period through the March 13, 2021 data cutoff.

For the first updated efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second updated efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2 for both endpoints.

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 14).

Table 14. Updated Vaccine Efficacy Against Confirmed COVID-19 in Participants Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population (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)
16-55 years of age	52 3.593 (11517)	568 3.439 (11533)	91.2 (88.3, 93.5)
>55 years of age	25 2.499 (8194)	265 2.417 (8208)	90.9 (86.2, 94.2)

Source: STN 125742.032 c4591001-508-efficacy tables, Table H, Page 13
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: Participants 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 participants in the specified group.
[b.] n1 = Number of participants meeting the endpoint definition.
[c.] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk 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 participants at risk for the endpoint.
[e.] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

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 15).

Table 15. Updated Vaccine Efficacy Against Confirmed COVID-19 in Participants With or Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

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)
16-55 years of age	56 3.766 (12088)	584 3.619 (12142)	90.8 (87.9, 93.1)
>55 years of age	25 2.573 (8445)	270 2.492 (8453)	91.0 (86.5, 94.3)

Source: STN 125742.032 c4591001-508-efficacy tables, Table I, Page 14
Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
[a.] N = number of participants in the specified group.
[b.] n1 = Number of participants meeting the endpoint definition.
[c.] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk 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 participants at risk for the endpoint.
[e.] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Multiple Cases of COVID-19

Five placebo recipients developed 2 separate and clinically symptomatic instances of COVID-19 which were confirmed by NAAT at the central laboratory. Only the first occurrence of the confirmed COVID-19 illness was counted towards the updated VE analyses. All of the second confirmed COVID-19 cases occurred during the period before their first dose of BNT162b2 except for 1 participant developed their second COVID-19 diagnosis 4 days after his second dose of BNT162b2. All participants were N-binding antibody negative prior to their first instance of COVID-19. The time interval between the COVID-19 episodes varied from 1 to 5 months. Multiple cases of COVID-19 did not occur in vaccine recipients during the blinded portion of the study follow-up.

Subgroup Analyses

Subgroup analyses of the updated second vaccine efficacy endpoint provide additional information about the VE for participants with and without evidence of infection prior to vaccination in specific populations enrolled, which is the endpoint considered to represent the general population who may receive the vaccine, as prior infection status may not be known by vaccine recipients. The results are displayed below in Table 16. The VE point estimates for the subgroup analyses were comparable to results for the first primary efficacy endpoint.

VE point estimates were consistent across the subgroups examined with the exception of participants identifying as multiracial and participants with evidence of prior SARS-CoV-2 infection at enrollment, for which too few COVID-19 cases occurred to interpret efficacy data for these subgroups. Additionally, the numbers of participants and cases in some other specific subgroups, such as the adolescent age group and racial subgroups, limits the interpretability of the VE results because of the wide credible intervals, but are displayed for completeness.

Table 16. Subgroup Analyses of Second Primary Endpoint, by Demographic and Baseline Characteristics: Updated Vaccine Efficacy Against Confirmed COVID-19 in Participants With or Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

	Vaccine Group (as Randomized)		
Subgroup	**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])**
Overall	81 6.340 (20533)	854 6.110 (20595)	90.9 (88.5, 92.8)
Age group: 16-17 years	0 0.065 (365)	11 0.061 (355)	100.0 (62.4, 100.0)
Age group: 18-64 years	74 5.008 (15853)	715 4.817 (15914)	90.0 (87.3, 92.3)
Age group: ≥65 years	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
Age group: 65-74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
Age group: ≥75 years	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)
Sex: Female	37 3.051 (9985)	455 3.013 (10241)	92.0 (88.8, 94.4)
Sex: Male	44 3.289 (10548)	399 3.097 (10354)	89.6 (85.8, 92.6)
Ethnicity: Hispanic or Latino	32 1.841 (5280)	240 1.777 (5266)	87.1 (81.3, 91.4)
Ethnicity: Not Hispanic or Latino	48 4.466 (15149)	614 4.300 (15220)	92.5 (89.9, 94.5)
Ethnicity: Not reported	1 0.032 (104)	0 0.034 (109)	-∞ (NA, NA)
Race: American Indian or Alaska native	0 0.043 (196)	3 0.038 (180)	100.0 (-116.0, 100.0)
Race: Asian	3 0.258 (907)	24 0.247 (896)	88.0 (60.6, 97.7)
Race: Black or African American	4 0.602 (1909)	49 0.591 (1928)	92.0 (78.1, 97.9)
Race: Native Hawaiian or other Pacific Islander	0 0.016 (54)	1 0.008 (31)	100.0 (-1947.9, 100.0)
Race: White	69 5.234 (16846)	749 5.054 (16952)	91.1 (88.6, 93.2)
Race: Multiracial	5 0.160 (538)	22 0.140 (503)	80.1 (46.1, 94.1)
Race: Not reported	0 0.027 (83)	6 0.031 (105)	100.0 (1.4, 100.0)
Baseline SARS-CoV-2 Status:Positive[h]	3 0.183 (593)	6 0.195 (643)	46.7 (-149.5, 91.4)
Baseline SARS-CoV-2 Status:Negative[i]	77 6.119 (19805)	846 5.883 (19838)	91.2 (88.9, 93.2)
Baseline SARS-CoV-2 Status:Unknown	1 0.038 (135)	2 0.033 (114)	56.9 (-728.5, 99.3)
Country: Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Country: Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)

	Vaccine Group (as Randomized)		
Subgroup	**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])**
Country: Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
Country: South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Country: Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
Country: United States	51 4.692 (15626)	645 4.515 (15691)	92.4 (89.9, 94.4)

Source: STN 125742.032 c4591001-508-efficacy tables, Table J, Page 15
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.
[a.] N = number of participants in the specified group.
[b.] n1 = Number of participants meeting the endpoint definition.
[c.] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk 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 participants at risk for the endpoint.
[e.] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
[f.] Includes participants who had at least one of the Charlson Comorbidity Index category (see Appendix A) or obesity (BMI ≥30 kg/m2).
[g.] Participants (≥16 years of age) who had BMI ≥30 kg/m2.
[h.] Positive N-binding ant body result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
[i.] Negative N-binding ant body result and negative NAAT result at Visit 1 and no medical history of COVID-19.

The subgroup analyses of updated vaccine efficacy by risk status in participants are presented in Table 17.

Table 17. Subgroup Analyses of Second Primary Endpoint, by Risk Status: Updated Vaccine Efficacy Against Confirmed COVID-19 in Participants With or Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

	Vaccine Group (as Randomized)		
Subgroup	**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])**
Overall	81 6.340 (20533)	854 6.110 (20595)	90.9 (88.5, 92.8)
At risk: Yes[f]	36 2.887 (9359)	402 2.772 (9340)	91.4 (87.9, 94.1)
At risk: No	45 3.453 (11174)	452 3.338 (11255)	90.4 (86.9, 93.1)
Age group and Risk: 16-64 and not at risk	44 2.887 (9254)	397 2.779 (9289)	89.3 (85.4, 92.4)
Age group and Risk: 16-64 and at risk	30 2.186 (6964)	329 2.100 (6980)	91.2 (87.3, 94.2)
Age group and Risk: ≥65 and not at risk	1 0.566 (1920)	55 0.559 (1966)	98.2 (89.6, 100.0)
Age group and Risk: ≥65 and at risk	6 0.701 (2395)	73 0.672 (2360)	92.1 (82.0, 97.2)
Obese: Yes[g]	28 2.185 (6999)	314 2.139 (7111)	91.3 (87.1, 94.3)

	Vaccine Group (as Randomized)		
Subgroup	**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])**
Obese: No	53 4.153 (13528)	540 3.970 (13478)	90.6 (87.5, 93.1)
Age group and obese:16-64 and not obese	49 3.303 (10629)	458 3.158 (10614)	89.8 (86.2, 92.5)
Age group and obese:16-64 and obese	25 1.768 (5584)	268 1.719 (5649)	90.9 (86.3, 94.2)
Age group and obese: ≥65 and not obese	4 0.850 (2899)	82 0.811 (2864)	95.3 (87.6, 98.8)
Age group and obese: ≥65 and obese	3 0.417 (1415)	46 0.420 (1462)	93.4 (79.5, 98.7)

Source: STN 125742.032 c4591001-508-efficacy tables, Table J, Page 15
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.
[a.] N = number of participants in the specified group.
[b.] n1 = Number of participants meeting the endpoint definition.
[c.] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk 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 participants at risk for the endpoint.
[e.] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
[f.] Includes participants who had at least one of the Charlson Comorbidity Index category (see Appendix A) or obesity (BMI ≥30 kg/m2).
[g.] Participants (≥16 years of age) who had BMI ≥30 kg/m2.
[h.] Positive N-binding ant body result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
[i.] Negative N-binding ant body result and negative NAAT result at Visit 1 and no medical history of COVID-19.

Participants with positive prior SARS-CoV-2 status at baseline were defined as those with positive N-binding antibody or NAAT results at Visit 1 or a medical history of COVID-19. In the evaluable efficacy analysis for this subgroup, the estimated VE against cases occurring ≥7 days after Dose 2 was 46.9% (3 cases BNT162b2; 6 cases placebo), and in the all-available efficacy analysis the estimated VE against cases occurring at any time after Dose 1 was 19.2% (13 cases BNT162b2, 17 cases placebo). The low baseline seropositivity rate and small number of cases that occurred in these participants limits the interpretation of these data but indicate that symptomatic re-infections did occur among participants who were previously infected.

Additional analyses of the updated vaccine efficacy endpoint were conducted to evaluate the vaccine efficacy, by demographic characteristics, geographic area, and comorbidity status, as displayed above in Section 6.1.11.1. VE point estimates were uniformly high across the comorbidities examined, though interpretation of some of the results is limited by small numbers of participants and/or cases.

The demographics of the participants with confirmed COVID-19 cases contributing to the updated vaccine efficacy analysis are displayed below in Table 18.

Table 18. Demographic Characteristics of Participants With Protocol-Defined COVID-19, Participants Without Evidence of Prior SARS-CoV-2 Infection

	Vaccine Group (as Randomized)		
Characteristic	**BNT162b2 (N[a] =77) n[b] (%)**	**Placebo (N[a] =833) n[b] (%)**	**Total (N[a] =910) n[b] (%)**
Age at Vaccination: Mean years (SD)	46.9 (14.79)	47.1 (15.58)	47.1 (15.51)
Age at Vaccination: Median (years)	50.0	47.0	48.0
Age at Vaccination: Min, max (years)	(19, 77)	(16, 88)	(16, 88)
Age Group: 16-17 years	0	10 (1.2)	10 (1.1)
Age Group: 18-64 years	70 (90.9)	699 (83.9)	769 (84.5)
Age Group: ≥65 years	7 (9.1)	124 (14.9)	131 (14.4)
Age Group: 65-74 years	6 (7.8)	98 (11.8)	104 (11.4)
Age Group: ≥75 years	1 (1.3)	26 (3.1)	27 (3.0)
Race: American Indian or Alaska Native	0	3 (0.4)	3 (0.3)
Race: Asian	3 (3.9)	23 (2.8)	26 (2.9)
Race: Black or African American	4 (5.2)	48 (5.8)	52 (5.7)
Race: Native Hawaiian or Other Pacific Islander	0	1 (0.1)	1 (0.1)
Race: White	67 (87.0)	730 (87.6)	797 (87.6)
Race: Multiracial	3 (3.9)	22 (2.6)	25 (2.7)
Race: Not reported	0	6 (0.7)	6 (0.7)
Sex: Female	35 (45.5)	444 (53.3)	479 (52.6)
Sex: Male	42 (54.5)	389 (46.7)	431 (47.4)
Ethnicity: Hispanic or Latino	29 (37.7)	236 (28.3)	265 (29.1)
Ethnicity: Not Hispanic or Latino	47 (61.0)	597 (71.7)	644 (70.8)
Ethnicity: Not reported	1 (1.3)	0	1 (0.1)
Comorbidities: Yes[c]	35 (45.5)	395 (47.4)	430 (47.3)
Comorbidities: No	42 (54.5)	438 (52.6)	480 (52.7)
Obesity: Yes[d]	27 (35.1)	310 (37.2)	337 (37.0)
Obesity: No	50 (64.9)	523 (62.8)	573 (63.0)
Country: Argentina	15 (19.5)	108 (13.0)	123 (13.5)
Country: Brazil	12 (15.6)	80 (9.6)	92 (10.1)
Country: Germany	0	1 (0.1)	1 (0.1)
Country: South Africa	0	9 (1.1)	9 (1.0)
Country: Turkey	0	5 (0.6)	5 (0.5)
Country: United States	50 (64.9)	630 (75.6)	680 (74.7)

Source: STN 125742.032 c4591001-508-efficacy tables, Table K, Page 22

[a.] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.

[b.] n = Number of participants with the specified characteristic.

[c.] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index category (see Appendix A) or BMI ≥30 kg/m^2.

[d.] Participants who had BMI ≥30 kg/m^2.

Additional analyses of the updated vaccine efficacy endpoint were conducted to evaluate the vaccine efficacy by comorbidity status. VE point estimates were uniformly high across the comorbidities examined, though interpretation of some of the results is limited by small numbers of participants and/or cases Table 19.

Table 19. Updated Vaccine Efficacy by Comorbidity Status, Participants Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

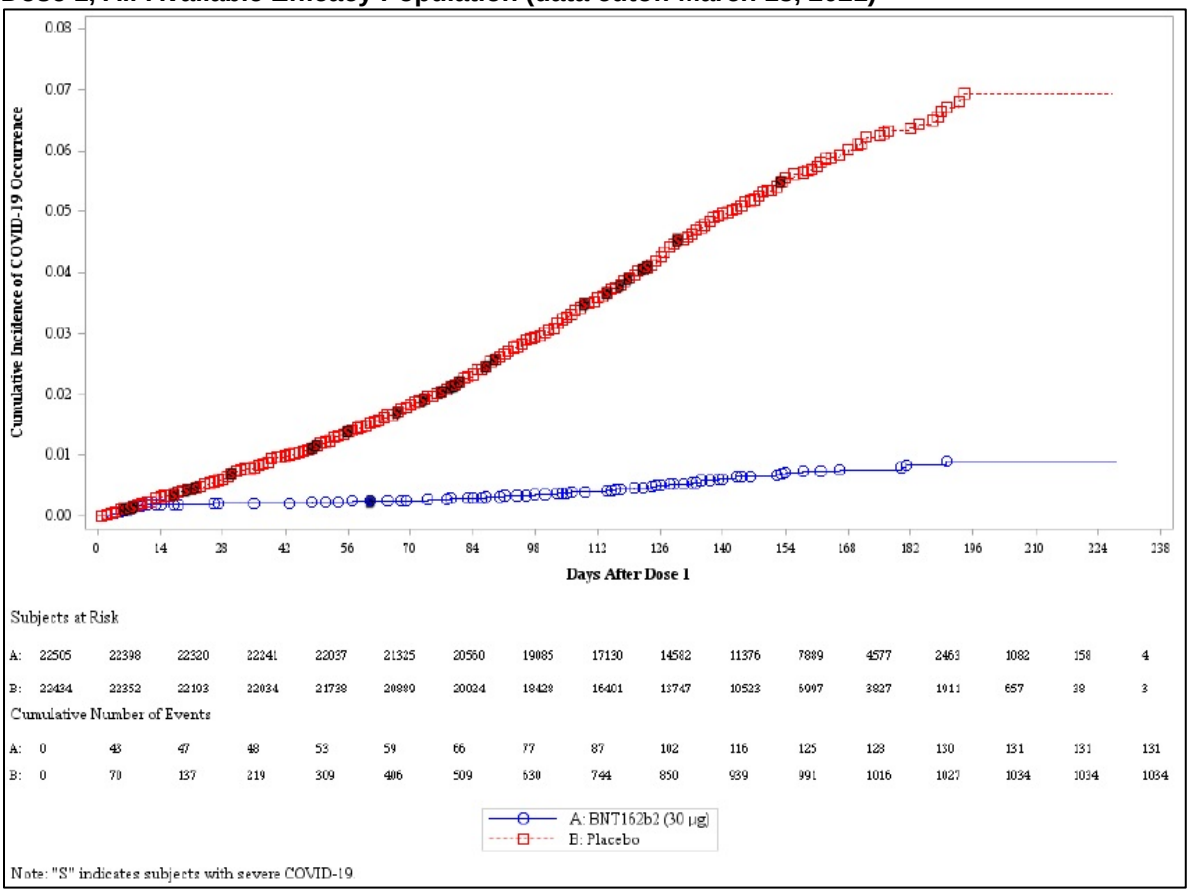
	Vaccine Group (as Randomized)		
Subgroup	**BNT162b2 (N[a] =19993) Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo (N[a] =20118) Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy (%) (95% CI[e])**
Overall	77 6.092 (19711)	833 5.857 (19741)	91.1 (88.8, 93.1)
Comorbidity			
No comorbidity	42 3.329 (10757)	438 3.207 (10808)	90.8 (87.3, 93.4)
Any comorbidity[f]	35 2.763 (8954)	395 2.65 (8933)	91.5 (88.0, 94.2)
Cardiovascular	3 0.172 (584)	22 0.159 (555)	87.4 (58.1, 97.6)
Chronic pulmonary disease	8 0.474 (1582)	66 0.443 (1562)	88.7 (76.3, 95.3)
Diabetes	9 0.465 (1528)	60 0.444 (1513)	85.7 (70.9, 93.7)
Obese (≥30.0 kg/m^2)	27 2.083 (6673)	310 2.034 (6770)	91.5 (87.4, 94.5)
Hypertension	15 1.481 (4900)	190 1.427 (4895)	92.4 (87.1, 95.8)
Diabetes (including gestational diabetes)	9 0.468 (1537)	62 0.447 (1527)	86.1 (71.9, 93.9)

Source: STN 125742.032 c4591001-508-efficacy tables, Table L, Page 25
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: Participants 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 participants in the specified group.
[b.] n1 = Number of participants meeting the endpoint definition.
[c.] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk 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 participants at risk for the endpoint.
[e.] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
[f.] Subject who had 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index category (see Appendix A) or BMI ≥30 kg/m^2.

Cumulative incidence curves

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1, (Figure 3), COVID-19 disease onset appears to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, at which time point, the curves diverge.

Figure 3. Updated Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, All-Available Efficacy Population (data cutoff March 13, 2021)



Source: Adapted from STN 125742.0 c4591001-interim-mth6-report-body.pdf. Figure 2. page 104.

An updated analysis of the number of confirmed COVID-19 cases following Dose 1 was conducted with the all-available efficacy population, for all participants regardless of evidence of prior infection through 7 days after Dose 2, and at time intervals following completion of the vaccine series (Table 20).

Table 20. Updated Vaccine Efficacy after Dose 1, Dose 1 All-Available Efficacy Population

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 (68.0, 98.1)
≥7 Days after Dose 2	82 6.479 (21019)	870 6.207 (20901)	91 (88.7, 92.9)
≥7 Days after Dose 2 to <2 Months after Dose 2	12 2.786 (21019)	296 2.750 (20901)	96.0 (92.9, 98)

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]
≥2 Months after Dose 2 to 4 Months after Dose 2	46 2.665 (20160)	446 2.564 (19720)	90.1 (86.5, 92.8)
≥4 Months after Dose 2	24 1.028 (12624)	128 0.893 (11760)	83.7 (74.7, 89.9)

Source: STN 125742.032 c4591001-508-efficacy tables, Table O, Page 30
Abbreviation: VE = vaccine efficacy.
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk 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 participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

The VE estimate for the prevention of COVID-19 disease after Dose 1 in the all-available efficacy population is 87.6%. Additionally, VE at ≥4 Months after Dose 2 is 83.7% in the all-available efficacy population, suggesting some modest attenuation in efficacy over time. However, this attenuation was limited to efficacy against non-severe COVID-19, as the only protocol-confirmed severe case reported during blinded, placebo-controlled follow-up among BNT162b2 recipients in the all-available efficacy population occurred with onset at 35 days after Dose 2 and did not result in hospitalization (see Section 6.1.11.2 for further details). Based on the number of cases accumulated after Dose 1 and before Dose 2, there does seem to be some protection against COVID-19 disease following one dose; however, these data do not provide information about longer term protection beyond 3 weeks after a single dose. VE estimates over these time intervals in the all-available efficacy population were similar to estimates in the evaluable efficacy population.

Additional analyses assessed vaccine efficacy in two successive periods of follow-up, from days 35-90 and 91-224, to explore whether changes in COVID-19 epidemiology or potential waning of immunity during the blinded follow-up period may have impacted vaccine efficacy over time. Vaccine efficacy for days 35-90 and days 91-224 were 93.7% [90.6;96.0] and 88.3% [84.6;91.2], respectively. The risk ratio of the incidence rates between vaccine and placebo in the period from Dose 1 to Day 57 and from Dose 1 to Day 224 were 0.173 [95% CI 0.128;0.232] and 0.122 [95% CI 0.101;0.147], suggesting a small, non- significant change in vaccine efficacy over time.

> *Reviewer Comment:* Updated efficacy analyses were conducted in March 2021, prior to the emergence of the B.1.617.2 (Delta) variant in the US.

6.1.11.2 Analyses of Secondary Endpoints

In the protocol-specified event-driven final analysis of the evaluable efficacy population, vaccine efficacy against severe COVID-19 for participants without prior SARS-CoV-2 infection occurring at least 7 days after Dose 2 was 66.4% (95% Credible Interval: -124.8%, 96.3%). In this analysis, only four participants had severe COVID-19 disease at least 7 days after Dose 2 (1 BNT162b2 group; 3 placebo group). Please refer to the EUA Review Memo for additional details from that analysis time point.

Updated efficacy analyses of the secondary efficacy endpoint for prevention of severe COVID-19 were also evaluated with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through March 13, 2021. Vaccine efficacy against severe COVID-19 is presented in Table 21 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 severe COVID-19 cases in one participant who received BNT162b2 and 21 participants who received placebo. 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 based on a larger number of severe cases now show more compelling protection against severe COVID-19 disease offered by BNT162b2. The vaccine recipient who had severe COVID-19 disease met the severe case definition because oxygen saturation at the COVID-19 illness visit was 93% on room air. COVID-19 symptoms began 35 days after Dose 2. The participant was <55 years of age, not hospitalized, did not seek further medical care, and did not have risk factors for severe disease. Additional details about the severe cases in placebo recipients are discussed below, with the all-available efficacy population.

Table 21. Updated Vaccine Efficacy Against Severe COVID-19, Participants Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

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)

Source: STN 125742.032 c4591001-508-efficacy tables, Table M, Page 28
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: Participants 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 participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk 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 participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

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) (Table 22).

Table 22. Updated Vaccine Efficacy Against First Occurrence of Severe COVID-19 After Dose 1, Dose 1 All-Available Efficacy Population

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 (14.6, 100.0)
Dose 2 to 7 days after Dose 2	0 0.403 (21056)	1 0.402 (20962)	100 (-3783.8, 100.0)
≥7 days after Dose 2	1 6.493 (21029)	23 6.337 (20940)	95.8 (73.9, 99.9)

Source: STN 125742.032 c4591001-508-efficacy tables, Table N, Page 29
Abbreviation: VE = vaccine efficacy.
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk 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 participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

The 30 placebo recipients who had severe COVID-19 had a mean age of 51 years, with a range of 19 to 71 years of age. The demographics of these 30 participants are as follows: 17 (56.7%) participants were in the younger age group, 20 (66.7%) were male, 11 (36.7%) identified as Hispanic or Latinx, 15 (50%) were obese, and 9 (30%) had other comorbidities that increased the risk for severe disease. Ten (33.3%) participants were on high flow oxygen, 8 (26.7%) were admitted to the ICU, 2 (6.7%) were on a ventilator, and 1 participant died with septic shock while hospitalized for severe COVID 19.

6.1.11.4 Dropouts and/or Discontinuations

The number of participants who dropped out and/or discontinued from the study did not affect the interpretation of the vaccine efficacy outcomes. Refer to Section 6.1.12.7 for details regarding dropouts and/or discontinuations.

6.1.11.5 Exploratory and Post Hoc Analyses

Sequencing Data from Centrally Confirmed COVID-19 Cases

During the Phase 2/3 portion of Study C4591001 (July 27, 2020, through the data cutoff date of March 13, 2021), new SARS-CoV-2 variants emerged in geographical regions where the study was conducted. In a post hoc analysis, whole genome sequencing was performed for confirmed cases of COVID-19 evaluated for efficacy during the blinded placebo-controlled follow-up period up to the data cutoff date of March 13, 2021. SARS-CoV-2 variants of concern identified from COVID-19 cases in this study include B.1.1.7 (Alpha) and B.1.351 (Beta). Representation of identified variants among cases in vaccine versus placebo recipients did not suggest decreased vaccine effectiveness against these variants.

Table 23 below displays the sequence analysis summary for all SARS-CoV-2 lineages associated with confirmed COVID-19 cases in the BNT162b2 and placebo groups, including any designated as variants of concern (VOCs) or variants of interest (VOIs), based on WHO and CDC SARS CoV-2 variant classifications and definitions (World Health Organization 2021b; CDC 2021g). The designation as "Other" indicates that the sequenced SARS CoV-2 lineages were not considered VOCs or VOIs.

Table 23. SARS-CoV-2 Variants of Concern or Variants of Interest for the First COVID-19 Occurrence From 7 Days After Dose 2, Blinded Placebo-Controlled Follow-up Period, Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)		
SARS-CoV-2 Lineage[b] (Location First Identified)	**BNT162b2 (30 µg) (N[a] =81) n[c](%)**	**Placebo (N[a] =873) n[c](%)**	**Total (N[a] =954) n[c](%)**
B.1.1.7 (United Kingdom)	0	3 (0.3)	3 (0.3)
B.1.351 (South Africa)	0	9 (1.0)	9 (0.9)
B.1.427/B.1.429 (USA)	1 (1.2)	23 (2.6)	24 (2.5)
B.1.525 (UK and Nigeria)	0	1 (0.1)	1 (0.1)
B.1.526 (USA)	0	1 (0.1)	1 (0.1)
B.1.616 (France)	0	0	0
B.1.617 (India)	0	0	0
B.1.618 (India)	0	0	0
P.1 (Brazil/Japan)	1 (1.2)	1 (0.1)	2 (0.2)
P.2 (Brazil)	6 (7.4)	40 (4.6)	46 (4.8)
P.3 (Philippines)	0	0	0
Other	66 (81.5)	755 (86.5)	821 (86.1)
Unknown[d]	7 (8.6)	33 (3.8)	40 (4.2)
Not sequenced	0	8 (0.9)	8 (0.8)

Source: STN 125742.6 c4591001-sequencing-report.pdf, Table 1, page 11.
Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
[a]. N = number of subjects with first COVID-19 occurrence. This value is the denominator for the percentage calculations.
[b]. Based on PANGO lineages (cov-lineages.org).
[c]. n = Number of subjects with the specified characteristic.
[d]. Include indeterminate result and not quantifiable samples.

Reviewer Comment: The updated efficacy analyses were done prior to the emergence of the B.1.617.2 (Delta) variant in the US.

Updated Vaccine Efficacy Against Severe COVID-19, CDC definition

The Applicant conducted an additional updated analysis of vaccine efficacy against severe cases of COVID-19 using the CDC definition of severe COVID-19 (hospitalization, admission to the ICU, intubation or mechanical ventilation, or death), based on confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through March 13, 2021. Among participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, the estimated VE against CDC-defined severe COVID-19 occurring at least 7 days after Dose 2 was 100.0% (2-sided 95% CI: 88.1%, 100.0%), with 0 and 31 cases in the BNT162b2 and placebo groups, respectively. This additional analysis further supports the conclusion that BNT162b2 offers protection against severe COVID-19 disease.

6.1.12 Safety Analyses

The Phase 2/3 safety data presented in this section are categorized in following time periods:

1. Blinded placebo-controlled period: Dose 1 to 1 month after Dose 2 and to unblinding date:
   - Participants with up to ~6 months after Dose 2 (N=43,847; BNT162b2 group N=21,926 and placebo group N=21,921).
   - Solicited local ARs and systemic AEs were assessed during this time period from a subset of participants.
2. Open-label observational period: from time of unblinding to data cutoff date:
   - Participants originally randomized to BNT162b2 (N=20,309)
   - Participants originally randomized to placebo who then received BNT162b2 (N=19,525)
   - Participants originally randomized to placebo who had confirmed COVID-19 then received BNT162b2 (N=852)
   - Only unsolicited AEs (AEs, SAEs and adverse events of special interest [AESIs]) were assessed during this time period.
3. Cumulative follow-up from Dose 1 to at least 6 months after Dose 2:
   - Participants originally randomized to BNT162b2 (inclusive of blinded data and open-label data through the March 13, 2021 data cutoff). (Total N=12,006: 16-55 years of age/younger age group [N =6,666] and >55 years of age/older age group [N =5,340]).

   Reviewer Comment: Interpretation of safety data from the open-label observational period are limited because there was no longer a study group for safety comparisons in the unblinded portion of the study. Additionally, 839 of the initial randomized placebo recipients (610 in the younger age group and 229 in the older age group) either opted not to receive vaccine after unblinding or had not had the opportunity to receive BNT162b2 at the time of the March 13, 2021 data cutoff.

Participants with chronic, stable HIV infection were excluded from the general safety population analyses and are summarized in a separate analysis (see Section 9.1.6 of this memo).

6.1.12.1 Methods

Please see Section 6.1.7.

6.1.12.2 Overview of Adverse Events

Overview of adverse events

Table 24 below presents an overview of immediate unsolicited adverse events and solicited local reactions and systemic adverse events in the safety population. Table 25 below presents an overview of participants reporting at least 1 unsolicited adverse event during the blinded placebo-controlled time period.

In the blinded placebo-controlled time period, the most frequently reported solicited adverse reactions in all age groups included injection site pain, fatigue, headache, muscle pain, and chills. Additionally, unsolicited ARs reported at higher frequency by

the BNT162b2 group than the placebo group among participants not included in the reactogenicity subset were consistent with local and systemic adverse reactions adverse reactions solicited among participants in the reactogenicity subset.

Table 24. Immediate and Solicited Local Reactions and Systemic Adverse Events, Participants 16 Years of Age and Older, Safety Population

Event	BNT162b2 n[a]/N[b] (%)	Placebo n[a]/N[b] (%)
Immediate unsolicited AE within 30 minutes after vaccination		
Dose 1	105/21926 (0.5)	81/2191 (0.4)
Dose 2	71/21571 (0.3)	54/21549 (0.3)
Solicited local reaction within 7 days		
Dose 1	3877/4907 (79.0)	639/4897 (13.0)
Dose 2	3351/4542 (73.8)	483/4517 (10.7)
Solicited systemic AE within 7 days		
Dose 1	2963/4907 (60.4)	2308/4897 (47.1)
Dose 2	3237/4542 (71.3)	1542/4517 (34.1)

Source: STN 125742.0.37 c4591001-508-safety-tables.pdf, Table P, page 12.
Note: MedDRA (v23.1) coding dictionary applied.
Note: Immediate AE refers to an AE reported in the 30-minute observation period after vaccination.
[a]n = Number of subjects reporting at least 1 occurrence of the specified event category.
[b] N: number of participants in the specified age group in the reactogenicity subset of the safety population with data available for the adverse event. .

Table 25. Unsolicited Adverse Events, Blinded Placebo-controlled Follow-up Period, Participants 16 Years of Age and Older, Safety Population

Adverse Event	BNT162b2 16-55 Years (N[a]=12995) n[b] (%)	BNT162b2 >55 Years (N[a]=8931) n[b] (%)	BNT162b2 Total (N[a]=21926) n[b] (%)	Placebo 16-55 Years (N[a]=13026) n[b] (%)	Placebo >55 Years (N[a]=8895) n[b] (%)	Placebo Total (N[a]=21921) n[b] (%)
Dose 1 through 1 Month after Dose 2						
Any unsolicited AE	4233 (32.6)	2384 (26.7)	6617 (30.2)	1871 (14.4)	1177 (13.2)	3048 (13.9)
Unsolicited non-serious AE	4207 (32.4)	2350 (26.3)	6557 (29.9)	1855 (14.2)	1141 (12.8)	2996 (13.7)
SAEs	52 (0.4)	75 (0.8)	127 (0.6)	49 (0.4)	67 (0.8)	116 (0.5)
Withdrawal due to unsolicited AE	19 (0.1)	13 (0.1)	32 (0.1)	20 (0.2)	16 (0.2)	36 (0.2)
Death	0 (0.0)	3 (0.0)	3 (0.0)	2 (0.0)	3 (0.0)	5 (0.0)
Dose 1 to cutoff date or participant unblinding (whichever is earlier)						
Any unsolicited AE	4396 (33.8)	2551 (28.6)	6947 (31.7)	2136 (16.4)	1432 (16.1)	3568 (16.3)
Unsolicited non-serious AE	4347 (33.5)	2471 (27.7)	6818 (31.1)	2086 (16.0)	1347 (15.1)	3433 (15.7)
SAE	103 (0.8)	165 (1.8)	268 (1.2)	117 (0.9)	151 (1.7)	268 (1.2)
Withdrawal due to unsolicited AE	22 (0.2)	23 (0.3)	45 (0.21)	28 (0.2)	23 (0.3)	51 (0.2)
Death	3 (0.0)	12 (0.1)	15 (0.1)	4 (0.0)	10 (0.1)	14 (0.1)

Source: STN 125742.0, amendment 66. Response to IR.
N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
Cutoff date: March 13, 2021; unblinding date varied depending on subject contact date for unblinding.

Immediate AEs

The frequency of immediate AEs (defined as events occurring within the first 30 minutes following any dose) reported in the vaccine group was 0.5% after Dose 1 and 0.3% after Dose 2 and were mainly consistent with solicited reactogenicity events. In both study groups, the most frequently reported immediate AE was injection site pain (BNT162b2 vaccine 0.3%, placebo 0.2%). For both study groups, no participant reported an immediate allergic reaction that was considered by the study investigator to be related to vaccination or to the saline placebo.

Reviewer Comment: FDA agrees with the study investigators' assessment.

Anaphylaxis

No anaphylactic reactions to BNT162b2 were reported through the cutoff date of March 13, 2021. During the open-label observational follow-up period for study C4591001, among participants ≥16 years of age, 1 participant who received BNT162b2 as Dose 3 (crossover vaccination as subject was originally randomized to placebo) experienced an SAE of anaphylactoid reaction, which was assessed as related to study vaccine. The subject, a female adolescent with a medical history significant for multiple allergies since infancy reported that 2 days after receiving BNT162b2, the appearance of hives on her left arm (deltoid). Approximately 24 minutes after the appearance of the hives she self-administered an epinephrine pen (personal medication given the history of anaphylaxis to multiple allergens). Six minutes after injection, the subject experienced shortness of breath. Hives and shortness of breath resolved within 10 and 30 minutes, respectively, of epinephrine treatment. The subject did not seek additional medical attention. As a result of the anaphylactoid reaction, the subject was permanently withdrawn from the study (FDA 2021b).

During the blinded placebo-controlled follow-up period, three SAEs involving allergic reactions were reported among three participants ≥16 years of age (previously reported at November 14, 2020 cutoff date). A review of the temporal relationship to vaccination and alternate inciting etiology does not support the administration of BNT162b as the causative agent:

- Anaphylactic reaction following a bee sting in a BNT162b2 recipient (8 days after Dose 2)
- Drug hypersensitivity to an antibiotic in a BNT162b2 recipient (9 days after Dose 2)
- Anaphylactic shock due to an ant bite in a placebo recipient (18 days after Dose 2).

Solicited local reactions and systemic adverse events

Solicited Local Reactions

For each age group in the reactogenicity subset (younger: 16-55 years, older: >55 years) and overall (16 years and older), the median onset of solicited local reactions in the vaccine group was 0 (day of vaccination) to 2 days after either dose and solicited reactions lasted a median duration between 1 and 2 days.

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%) and also pain characterized as moderate (29.4% vs. 18.7%); a similar pattern was observed after Dose 1. Injection site redness and swelling after each dose were generally similar for both age groups.

Table 26 and Table 27 present the frequency and severity of reported solicited local reactions within 7 days following each dose of BNT162b2 and placebo in the subset of participants 16 55 years of age, and older than 55 years of age, respectively, included in the safety population who were monitored for reactogenicity with an electronic diary.

Subgroup analyses by age

Table 26. Frequency of Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, Participants 16 Through 55 Years of Age, Reactogenicity Subset of the Safety Population*

	BNT162b2 Dose 1 N[a] =2899 n[b] (%)	Placebo Dose 1 N[a] =2908 n[b] (%)	BNT162b2 Dose 2 N[a] =2682 n[b] (%)	Placebo Dose 2 N[a] =2684 n[b] (%)
Redness[c]				
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[c]				
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[d]				
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

Source: STN 125742.0 c4591001-interim-mth6-report-body.pdf, Table 14.68, pages 531-532.
Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
No Grade 4 solicited local reactions were reported in participants 16 through 55 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b.n = Number of participants with the specified reaction.
c. Mild: 2.0 to ≤5.0 cm; Moderate: 5.0 to ≤10.0 cm; Severe: >10.0 cm.
d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table 27. Frequency of Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, Participants Older Than 55 Years of Age, Reactogenicity Subset of the Safety Population*

	BNT162b2 Dose 1 N[a] =2008 n[b] (%)	Placebo Dose 1 N[a] =1989 n[b] (%)	BNT162b2 Dose 2 N[a] =1860 n[b] (%)	Placebo Dose 2 N[a] =1833 n[b] (%)
Redness[c]				
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)

	BNT162b2 Dose 1 N[a] =2008 n[b] (%)	Placebo Dose 1 N[a] =1989 n[b] (%)	BNT162b2 Dose 2 N[a] =1860 n[b] (%)	Placebo Dose 2 N[a] =1833 n[b] (%)
Swelling[c]				
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 (0.0)	4 (0.2)	1 (0.1)
Pain at the injection site[d]				
Any (>2.0 cm)	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 (0.0)	10 (0.5)	0 (0.0)

Source: STN 125742.0 c4591001-interim-mth6-report-body.pdf, Table 14.68, pages 532-534.
Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
No Grade 4 solicited local reactions were reported in participants 16 through 55 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b.n = Number of participants with the specified reaction.
c. Mild: 2.0 to ≤5.0 cm; Moderate: 5.0 to ≤10.0 cm; Severe: >10.0 cm.
d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Solicited Systemic Reactions

For each age group in the reactogenicity subset (younger: 16-55 years, older: >55 years) and overall (16 years and older), the median onset of solicited systemic AEs in the vaccine group in general was 1 to 2 days after either dose, and solicited systemic AEs lasted a median duration of 1 day.

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

Subgroup analyses by age

Table 28 and Table 29 present the frequencies and severities of reported solicited systemic reactions within 7 days following each dose of BNT162b2 and placebo in the subset of participants 16-55 years of age, and >55 years of age, respectively, included in the safety population who were monitored for reactogenicity with an electronic diary.

Table 28. Frequency of Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose, Participants 16 Through 55 Years of Age, Reactogenicity Subset of the Safety Population*

	BNT162b2 Dose 1 N[a] =2899 n[b] (%)	Placebo Dose 1 N[a] =2908 n[b] (%)	BNT162b2 Dose 2 N[a] =2682 n[b] (%)	Placebo Dose 2 N[a] =2684 n[b] (%)
Fever				
≥38.0℃	119 (4.1)	25 (0.9)	440 (16.4)	11 (0.4)
≥38.0℃ to 38.4℃	86 (3.0)	16 (0.6)	254 (9.5)	5 (0.2)
>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 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)

	BNT162b2 Dose 1 N[a] =2899 n[b] (%)	Placebo Dose 1 N[a] =2908 n[b] (%)	BNT162b2 Dose 2 N[a] =2682 n[b] (%)	Placebo Dose 2 N[a] =2684 n[b] (%)
Fatigue[c]				
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[c]				
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[c]				
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[d]				
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 (0.0)	1 (0.0)	4 (0.1)	0 (0.0)
Diarrhea[e]				
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[c]				
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[c]				
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[f]	805 (27.8)	398 (13.7)	1213 (45.2)	320 (11.9)

Source: STN 125742.0 c4591001-interim-mth6-report-body.pdf, Table 14.75, pages 553-557.
Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.
No Grade 4 solicited systemic reactions were reported in participants 16 through 55 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified reaction.
c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
f. Severity was not collected for use of antipyretic or pain medication.

Table 29. Frequency of Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose, Participants Older than 55 Years of Age, Reactogenicity Subset of the Safety Population*

	BNT162b2 Dose 1 N[a] =2008 n[b] (%)	Placebo Dose 1 N[a] =1989 n[b] (%)	BNT162b2 Dose 2 N[a] =1860 n[b] (%)	Placebo Dose 2 N[a] =1833 n[b] (%)
Fever				
≥38.0℃	26 (1.3)	8 (0.4)	219 (11.8)	4 (0.2)
≥38.0℃ to 38.4℃	23 (1.1)	3 (0.2)	158 (8.5)	2 (0.1)
>38.4℃ to 38.9℃	2 (0.1)	3 (0.2)	54 (2.9)	1 (0.1)
>38.9℃ to 40.0℃	1 (0.0)	2 (0.1)	7 (0.4)	1 (0.1)
>40.0℃	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[c]				
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[c]				
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[c]				
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[d]				
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
Diarrhea[e]				
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[c]				
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[c]				
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[f]	382 (19.0)	224 (11.3)	688 (37.0)	170 (9.3)

Source: STN 125742.0 c4591001-interim-mth6-report-body.pdf, Table 14.75, pages 557-562.
Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.
The only Grade 4 solicited systemic reaction reported in participants >55 years of age was fatigue.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified reaction.
c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
f. Severity was not collected for use of antipyretic or pain medication.

Unsolicited (non-serious and serious) AEs

Non-serious unsolicited AEs

Dose 1 through 1 month after Dose 2

A higher frequency of unsolicited, non-serious adverse events was reported in the vaccine group (29.9%) compared to placebo group (13.7%). These excess AEs in the vaccine group were primarily attributed to local reactions and systemic adverse events reported during the first 7 days following vaccination in participants not enrolled in the reactogenicity subset and are consistent with solicited reactions/events reported by reactogenicity subset participants. Table 30 below presents unsolicited adverse events reported by at least 1% of participants in any treatment group for the safety population, with the total number of events reported, in addition to the number of events that were graded as severe.

Table 30. Frequency of Any and Severe Unsolicited Adverse Events Occurring in ≥1% of Participants in Any Treatment Group From Dose 1 to 1 Month After Dose 2, Safety Population

System Organ Class Preferred Term	BNT162b2 (N=21926) Any n (%) Severe n (%)	Placebo (N=21921) Any n (%) Severe n (%)
Gastrointestinal disorders		
Diarrhea	248 (1.1) 4 (<0.1)	188 (0.9) 5 (<0.1)
Nausea	274 (1.2) 1 (<0.1)	87 (0.4) 2 (<0.1)
General disorders and administration site conditions		
Chills	1365 (6.2) 18 (0.1)	120 (0.5) 0
Fatigue	1463 (6.7) 24 (0.1)	379 (1.7) 2 (<0.1)
Injection site pain	2915 (13.3) 19 (0.1)	397 (1.8) 0 (<0.1)
Pain	628 (2.9) 9 (<0.1)	61 (0.3) 0
Pyrexia	1517 (6.9) 38 (0.2)	77 (0.4) 1 (<0.1)
Musculoskeletal and connective tissue disorders		
Arthralgia	268 (1.2) 4 (<0.1)	102 (0.5) 6 (<0.1)
Myalgia	1239 (5.7) 21 (0.1)	168 (0.8) 3 (<0.1)

System Organ Class Preferred Term	BNT162b2 (N=21926) Any n (%) Severe n (%)	Placebo (N=21921) Any n (%) Severe n (%)
Nervous system disorders		
Headache	1339 (6.1) 25 (0.1)	424 (1.9) 10 (<0.1)

Source: STN 125742.037 c4591001-508-safety tables, Table R, Page 18
MedDRA v23.1 coding dictionary applied.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
Data analysis cutoff date: March 13, 2021

Unsolicited AEs of clinical interest (serious and non-serious)

FDA independently conducted Standardised MedDRA Queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited adverse event Preferred Terms that could represent various diseases and conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune conditions were queried to evaluate the occurrence of unsolicited events in the vaccine and placebo groups during the various follow-up periods (blinded, placebo-controlled and open label).

Dose 1 to 1 month after Dose 2
The SMQs conducted on the Phase 2/3 safety population from Dose 1 to 1 month after Dose 2 revealed a slight numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group (272 participants [1.1%] reporting 234 events) compared with the placebo group (225 participants [0.9%] reporting 190 events). Review of the hypersensitivity-related events indicates that most events were classified as skin or subcutaneous disorders with a slightly increased incidence in the vaccine group when compared to the placebo group of 152 and 123 events, respectively. Rash was the most commonly noted skin finding with 60 events in the vaccine group and 46 events in the placebo group. No imbalances between treatment groups were evident for any of the other SMQs evaluated.

Reports of lymphadenopathy were imbalanced with notably more cases in the vaccine group (83, one of which was serious) vs. the placebo group (7). The majority of events were mild or moderate, with 3 severe events reported, all in the BNT162b2 group. The median onset of lymphadenopathy following BNT162b2 was 5.5 days for Dose 1, with a shorter median onset of 2 days following Dose 2 of BNT162b2. Median duration of lymphadenopathy was 5.5 days in the BNT162b2 group.

Dose 1 to data cutoff date or participant's unblinding date (whichever was earlier)
The previously noted imbalances between the vaccine and the placebo group for hypersensitivity-related adverse events and lymphadenopathy remained evident, as described above. Notable findings regarding other AEs of clinical interest reported during blinded, placebo-controlled follow-up are summarized below. Very small numerical imbalances between the vaccine and placebo groups for Optic neuritis (2 vaccine vs. 0 placebo) and Encephalopathy (2 vaccine vs. 0 placebo) involved adverse events that were not assessed as related to BNT162b2 by the investigator, and FDA review of the details of these adverse events did not identify a basis to conclude a

causal relationship. Otherwise, no imbalances in non-serious unsolicited AEs between treatment groups were evident for any of the other SMQs evaluated.

AEs of clinical interest

- *Cardiac Disorders*
  The overall occurrence of cardiac disorders was numerically greater in the BNT162b2 vaccine group when compared to the placebo group (87 to 78, respectively), but for both groups the numbers represented an occurrence rate of 0.4%, with more participants in the older age groups (>55 years of age) reporting cardiac disorders compared with the younger age groups. Within each age group, rates of cardiac disorders were similar between the BNT162b2 vaccine group and placebo group, with the exception of tachycardia, which occurred more frequently in the younger age group subjects who received BNT162b2. See Appendix B for a list of cardiac disorders that occurred from Dose 1 to date of unblinding among Phase 2/3 participants 16 years of age and older.

- *Bell's Palsy*
  Bell's palsy (facial paralysis) was reported by 4 participants in the BNT162b2 group and 2 participants in the placebo group. Onset of facial paralysis was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. In the placebo group, the onset of facial paralysis was Day 32 and Day 102.

- *Deafness*
  A total of 11 cases (6 in the BNT162b2 group and 5 in the placebo group) were reported that included the following preferred terms associated with deafness: deafness, deafness unilateral, deafness neurosensory, hypoacusis and sudden hearing loss. The toxicity grades were mostly mild (4 in the BNT162b2 group and 2 in placebo) or moderate (1 in the BNT162b2 group and 3 in placebo), with one being severe (BNT162b2 group). For BNT162b2 recipients, the age range was 43-65 years of age, with one event occurring 19 days after Dose 1 and onset ranging from 1-55 days after Dose 2. Two of the reported events were considered by investigators as possibly related to BNT162b2:
    - One female participant >55 years of age reported unilateral deafness which occurred 19 days after Dose 1 and resolved 9 days later. The participant was discontinued from study intervention and remained in the study for safety evaluation.
    - One female participant 16-55 years of age reported unilateral deafness and dizziness which occurred 1 day after Dose 2, which was ongoing at the time of the data cutoff.

  One report of sudden unilateral neurosensory deafness was still ongoing at the time of the data cutoff and occurred in a BNT162b2 recipient 55 days after Dose 2. The event was considered unlikely to be related to the study intervention by the investigator, and FDA agrees with this assessment.

- *Deep Vein Thrombosis (DVT) and Other Venous Thromboembolic Events*
  One BNT162b2 recipient and one placebo recipient reported DVT characterized as non-serious AEs. The BNT162b2 recipient developed a DVT in the leg 14 days after Dose 2, which resolved after 6 days and was assessed by the study investigator as unrelated to vaccination; no hematologic results or medical intervention details were provided. The placebo recipient developed a DVT in the leg 85 days after placebo

Dose 2 that resolved after 1 day and was attributed by the study investigator to metabolic causes. No further information was provided.

During the blinded placebo-controlled follow-up period, two subjects who received BNT162b2 experienced venous thromboembolic events following Dose 2 (coagulopathy at 150 days and ophthalmic vein thrombosis at 70 days after the last vaccination). No similar events were observed in the placebo cohort. Neither event was temporally related to vaccination; both events were considered not related to vaccination by FDA.

None of the above events were associated with thrombocytopenia per the Applicant.

- *Guillain-Barre syndrome*
  One male placebo recipient (baseline SARS-CoV-2 negative) ≤55 years of age reported the occurrence of Guillain-Barre syndrome, which was considered a SAE and ongoing at the data cutoff. No vaccine recipients reported AEs consistent with Guillain-Barre syndrome.

Open-label observational follow-up: from participant unblinding to the March 13, 2021 data cutoff
In independent FDA analyses of SMQs of non-serious AEs occurring in the unblinded follow-up period, there were no notable patterns of specific categories of AEs that would suggest a causal relationship to BNT162b2.

Original BNT162b2 recipients
Overall, 20,309 original BNT162b2 recipients were followed after unblinding. Of these, 243 (1.2%) participants reported any adverse event; 20 (0.1%) participants had at least 1 occurrence of an event that was considered related to the vaccine, and 43 (0.2%) participants had at least 1 occurrence of an event that was graded as severe.

Overall, the rates of AEs in all System Organ Classes (SOCs) after the unblinding date decreased or remained similar to those in the blinded placebo-controlled period. The most commonly reported events occurred in the SOC of Injury, poisoning and procedural complications with 40 (0.2%) participants reporting at least 1 event, and the Preferred Term (PT) Fall had the highest number of participants (n=10). The SOC of Vascular disorders was reported by 23 (0.1%) participants, with the PT Hypertension having the highest number of participants (n=17).

Of the 20 participants who reported at least 1 event considered related to the vaccine, the events were similar to reactogenicity events, reflecting AEs within 7 days of vaccination (n=3 participants) or events reported more than 7 days from vaccination indicating either recurrent or prolonged reactogenicity symptoms. Note that one participant can report multiple events.
The most common SOCs and PTs are listed below:

- 13 participants reported at least 1 event in the SOC General disorders and administration site conditions: Injection site pain (7), Fatigue (6), Chills (3), Pain, and Pyrexia (2 each) and 1 reported Injection site swelling.
- 6 participants reported at least 1 event in the SOC Nervous system disorders: Headache (5), Dizziness (2) and 1 reported Dysgeusia (altered/impaired taste).

- 4 participants reported at least 1 event in the SOC Musculoskeletal and connective tissue disorders: Myalgia (2) and 1 participant each reported Back pain and Pain in extremity.

Placebo recipients who were unblinded and received BNT162b2
Overall, 19,525 original placebo participants were unblinded and received BNT162b2. The number of participants reporting any AE and at least 1 related AE were 4,885/19,525 (2.5%) and 4,508/19,525 (2.3%), respectively. The number of participants reporting severe AEs was 142/19,525 (0.1%).

The comparison to participants randomized to BNT162b2 from Dose 1 to the unblinding date shows that the number of participants who reported any AE, at least 1 related AE and severe AE for participants who originally received placebo and then received BNT162b2 are slightly greater (4,885/19,525 [2.5%], 4,508/19,525 [2.3%], 142/19,525 [0.1%]) than the frequencies (6,947/21,926 [3.2%], 5,246/21,926 [2.4%], 356/21,926 [0.2%]) for participants who originally were randomized to BNT162b2, respectively.

Immediate adverse events after either BNT162b2 dose (Dose 3 or 4, for original placebo recipients), were low in frequency (0.6%) Most immediate AEs after BNT162b2 were primarily injection site reactions, with injection site pain (0.4%) most frequently reported. Additionally, the following other immediate AEs were assessed as related to the study intervention:

- 1 participant in the younger age group reported 2 immediate AEs of edema mouth and tongue edema (both mild in severity) after Dose 4. The AE of tongue edema resolved the same day and the AE of edema mouth resolved the following day.
- 1 participant in the younger age group reported an immediate AE of hypoesthesia oral (mild in severity) after Dose 3 and resolved the same day.
- 1 participant in the younger age group reported 3 immediate AEs of swelling face, allergy to vaccine, and flushing after Dose 3, which were all were moderate in severity. All 3 AEs resolved the following day. The participant also reported nausea and urticaria (hives abdomen) (both mild in severity) on the same day but were not immediate. The AE of nausea resolved the same day and the AE of urticaria resolved the following day.
- 1 participant in the older age group reported an immediate AE of urticaria (hive on back of neck; moderate in severity) after Dose 4 and was ongoing at the time of the data cutoff date.

FDA agrees with the investigator assessments of relatedness to the study interventions listed for the four participants above.

Bell's Palsy
Three female participants, all ≤55 years of age, who originally received placebo, reported facial paralysis within 3 to 8 days of receiving either Dose 1 or 2 of BNT162b2. One case had a duration of 12 days, and the other 2 were ongoing as of the data cutoff date.

> *Reviewer Comment:* While these reports are from uncontrolled, open-label follow-up, the temporal relationship suggests a potential causal association between the vaccine and rare occurrence of Bell's Palsy, though the lack of a control group limits the interpretation. Considering all of the available evidence, Bell's Palsy will remain

described in the US package insert as a potential, but unconfirmed, infrequent adverse reaction.

Placebo recipients who had COVID-19 occurrence after Dose 1 and then received BNT162b2 after unblinding

There were 852 participants who originally received placebo, had protocol-confirmed COVID-19 during the blinded follow-up period, and then received BNT162b2 after unblinding. Of these, 225 (26.4%) participants reported any adverse event; 211 (24.7%) participants had at least 1 occurrence of an event that was considered related to the vaccine, and 4 (0.5%) participants had at least 1 occurrence of an event that was graded as severe. Of note, per protocol, these participants did not receive an e-diary for solicited local and systemic reactogenicity following vaccine administration.

Most AEs reported from Dose 3 (the first dose of BNT162b2) to the data cutoff date were in SOCs with reactogenicity events and were consistent with the AEs reported in the BNT162b2 group in the blinded portion of the study:

- General disorders and administration site conditions (207 [24.3%])
- Musculoskeletal and connective tissue disorders (42 [4.9%])
- Nervous system disorders (58 [6.8%] including 52 listed with the PT Headache)
- Gastrointestinal disorders (15 [1.8%])

Reviewer Comment: Although collected with different methodology (solicited versus unsolicited and blinded versus unblinded), the events corresponding to solicited reactogenicity were not reported at higher frequencies or with greater severity following Dose 3 or Dose 4 in these participants with prior COVID-19 compared to solicited reactions following Dose 1 or Dose 2 in participants without prior COVID-19. Thus, these data do not suggest that reactogenicity is increased in individuals with prior symptomatic COVID-19.

<u>Placebo-controlled and Open-label follow up from Dose 1 to 6 Months after Dose 2: Original BNT162b2 Participants</u>

A total of 12,006 participants who originally received BNT162b2 had at least 6 months of follow-up post-Dose 2. Of these, 3,454 (28.8%) participants reported at least 1 AE, and 2,245 (18.7%) participants reported at least 1 related AE. The most frequently reported AEs were reactogenicity events: General disorders and administration site conditions reported in 2,016 (16.8%) (primarily injection site pain reported in 1,191 [9.9%], Pyrexia reported in 633 (5.3%), and Chills and Fatigue reported in 606 and 598 (both 5%), respectively, Musculoskeletal and connective tissue disorders reported in 905 (7.5%) (primarily Myalgia reported in 549 [4.6%] and Arthralgia reported in 153 [1.3%]), Nervous system disorders reported in 726 (6.0%) (primarily Headache reported in 572 [4.8%]), and Gastrointestinal disorders reported in 407 (3.4%). Additionally, the AE of lymphadenopathy in 29 (0.2%) was assessed by the investigator as related to the study intervention.

When frequencies of AEs for participants with at least 6 months of follow-up time are examined by time since the second dose, the frequency of AEs and related AEs is 25.8% and 18.6% through 1 month after Dose 2 compared with 4.8% and 0.1% from 1 month after Dose 2 to 6 months after Dose 2.

In the younger age group, the numbers of participants who reported at least 1 AE and 1 related AE from Dose 1 to 6 months after Dose 2 were 2013 (30.2%) and 1,386 (20.8%), respectively. In the older age group, the numbers of participants who reported at least 1 AE and 1 related AE from Dose 1 to 6 months after Dose 2 were 1,441 (27.0%) and 859 (16.1%), respectively. The most frequently reported AEs were reactogenicity events, as outlined in Table 31, below.

Table 31. Frequency of Unsolicited AEs with Occurrence in ≥1% From Dose 1 to 6 Months After Dose 2, Participants Who Originally Received BNT162b2 With at Least 6 Months of Follow-up Time, Safety Population

System Organ Class Preferred Term	16-55 Years N=6666 n (%)	>55 Years N=5340 n (%)	Total N=12006 n (%)
Any Event	2013 (30.2)	1441 (27)	3454 (28.8)
General disorders and administration site conditions	1246 (18.7)	770 (14.4)	2016 (16.8%)
Injection site pain	715 (10.7)	476 (8.9)	1191 (9.9)
Pyrexia	442 (6.6)	191 (3.6)	633 (5.3)
Fatigue	372 (5.6)	226 (4.2)	598 (5.0)
Chills	412 (6.2)	194 (3.6)	606 (5.0)
Pain	190 (2.9)	87 (1.6)	277 (2.3)
Musculoskeletal and connective tissue disorders	539 (8.1)	366 (6.9)	905 (7.5)
Myalgia	355 (5.3)	194 (3.6)	549 (4.6)
Arthralgia	84 (1.3)	69 (1.3)	153 (1.3)
Nervous system disorders	449 (6.7)	277 (5.2)	726 (6.0)
Headache	359 (5.4)	213 (4.0)	572 (4.8)
Gastrointestinal disorders	231 (3.5)	176 (3.3)	407 (3.4)
Diarrhea	69 (1.0)	54 (1.0)	123 (1.0)
Nausea	88 (1.3)	52 (1.0)	140 (1.2)
Infections and Infestations	161 (2.4)	134 (2.5)	295 (2.5)
Injury, Poisoning and Procedural Complications	100 (1.5)	107 (2.0)	207 (1.7)
Skin and Subcutaneous Tissue Disorders	80 (1.2)	73 (1.4)	153 (1.3)
Respiratory, Thoracic and Mediastinal Disorders	79 (1.2)	66 (1.2)	145 (1.2)

Source: FDA-generated.
MedDRA v23.1 coding dictionary applied.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.

From unblinding date to the data cutoff date, the number of participants who reported at least 1 AE was 243/20,309 (1.2%) in participants originally randomized to BNT162b2. Overall, the rates in all SOCs after the unblinding date decreased or remained similar to those in the blinded placebo-controlled period.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited or unsolicited in these subgroups were generally consistent with the overall study population.

Suspected COVID-19 Cases
As specified in the protocol, suspected cases of symptomatic COVID-19 that were not PCR-confirmed were not recorded as adverse events unless they met regulatory criteria for seriousness.

A total of 4,931 participants (2,285 in the BNT162b2 group and 2,636 in the placebo group) in the evaluable efficacy population for the second primary efficacy endpoint developed protocol-defined symptoms after 7 days post Dose 2 during the blinded follow-up period but were not counted as a confirmed case. Of these, 4,331 (87.8%) had negative PCR results (2,026 [88.7%] and 2,305 [87.1%] in the BNT162b2 and placebo groups, respectively). The remaining 699 (14.2% total; 303 [13.3%] and 396 [15%] in the BNT162b2 group and placebo groups, respectively) were not counted as a confirmed case because the PCR results were unknown or unavailable for the following reasons: the swab was not taken (477 [9.7%] total; 210 [9.2%] and 267 [10.1%] in the BNT162b2 group and placebo groups, respectively), the swab was taken outside of the symptom window (168 [3.4%] total; 80 [3.5%] and 88 [3.3%] in the BNT162b2 group and placebo groups, respectively) or the swab was taken, but results were not available (54 [1.1%%] total; 13 [0.6%] and 41 [1.5%] in the BNT162b2 group and place groups, respectively).

> *Reviewer Comment:* The number of participants who had COVID-19 symptoms but were not counted as a confirmed case because the PCR results were unknown or unavailable was small (n=699) and slightly higher in the placebo group (396 versus 303 in the BNT162b2 group). Excluding them from the efficacy analyses likely had minimal impact on VE results. Upon request, the Applicant provided a sensitivity analysis, and the average VE after imputation was over 70%, which was reassuring that these missing PCR results would not have a significant effect on the VE results. Please refer to the statistical review memo of vaccine efficacy for additional details of this analysis.

6.1.12.3 Deaths

From Dose 1 to the data cutoff (March 13, 2021), there were a total of 38 deaths among participants >16 years of age (19 BNT162b2 recipients, 2 Placebo/BNT162b2 recipients and 17 placebo recipients). A total of 29 deaths (15 BNT162b2, 14 placebo) occurred during the blinded, placebo-controlled period. There were more deaths in the population >55 years of age as expected due to increased age and comorbidities. The demographics for those that died in the study were representative of the study population as a whole.

A total of 21 participants (14 males/7 females; mean age 68 years) received at least one dose of BNT162b2 prior to their deaths. Deaths occurred 62 to 142 days following the last dose of vaccine. For the seventeen participants (9 male/8 female: mean age 60 years) who received at least one dose of placebo there were six cases of documented COVID-19 with deaths occurring ~93 days following vaccination. Table 32 below shows the subject age, cause of death and investigational product received for participants in the safety population. Seven deaths were due to COVID-19 (1 BNT162b2 recipient and 6 placebo recipients). Each case had a positive COVID test (PCR or NAAT), but not all tests (including the positive PCR in the case of fatal COVID-19 pneumonia reported 109 days after Dose 2 of BNT162b2) were within the specifications of the study protocol for tests with acceptable sensitivity and specificity and were therefore not included in

protocol-specified efficacy analyses of severe COVID-19 cases. Abbreviated narratives are provided for those participants who died from COVID-19 in Appendix C.

Cardiac conditions were reported as the cause of death for 9 participants (cardiac arrest [7], congestive heart failure [1] and cardiovascular disease [1] who had received at least one dose of BNT162b2. The time from the last dose of BNT-162b2 to a cardiac- related death was 25-128 days. The event occurring 25 days from Dose 1 BNT162b2 occurred in a subject who had previously received two doses of placebo and was classified as cardiopulmonary arrest secondary to aortic stenosis. In the placebo group there were 5 cardiac related deaths (2 myocardial infarction, 1 aortic rupture, 2 cardiac arrest) occurring 15-81 days following study intervention (placebo). This excludes deaths due to COVID-19 which may have included cardiac-related presentations as part of the clinical course.

> *Reviewer Comment:* Based on clinical review of the individual cases, the lack of a clear temporal association to vaccination, the presence of confounding factors (e.g., pre-existing comorbidities) and the small number of cases, FDA assessed these deaths as unlikely to be related to vaccination.

Table 32. Deaths from Dose 1 to Data Cutoff of March 13, 2021, Phase 2/3 Participants 16 Years of Age and Older, Safety Population

Vaccines Received	Age/Sex	Number of Doses	Time Since Last Dose (days)	Cause of Death
BNT162b2	56/F	2	62	Cardiac arrest
BNT162b2	54/M	2	87	Congestive heart failure
BNT162b2	64/M	2	90	MVA
BNT162b2	84/M	2	70	Cardiovascular disease
BNT162b2	77/M	2	120	Emphysematous cholecystitis and sepsis
BNT162b2	82/M	2	142	Metastatic pancreatic cancer
BNT162b2	63/F	2	69	COPD
BNT162b2	86/F	2	97	Septic shock due to bowel obstruction
BNT162b2	63/F	2	41	Sudden cardiac death
BNT162b2	58/F	2	72	Cardiac arrest
BNT162b2	51/M	2	112	Metastatic lung cancer
BNT162b2	53/M	2	85	Cardiopulmonary arrest
BNT162b2	78/F	2	128	Cardiac arrest
BNT162b2	76/M	2	30	Cardiac arrest
BNT162b2	58/M	2	116	Cardiac arrest following seizure &
BNT162b2	72/M	1	35	Shigella sepsis
BNT162b2	62/F	2	73	MVA^
BNT162b2	60/M	1	3	"Atherosclerosis" (Found dead at home)
BNT162b2	80/M	2	109	COVID pneumonia*
Placebo/ BNT162b2	84/M	2/ 1	25	Cardiopulmonary arrest secondary aortic stenosis
Placebo/ BNT162b2	67/M	2/ 1	4	Suicide
Placebo	67/M	2	86	Metastatic biliary cancer

Vaccines Received	Age/Sex	Number of Doses	Time Since Last Dose (days)	Cause of Death
Placebo	68/F	2	102	COVID-19* (respiratory failure)
Placebo	58/M	1	15	Myocardial infarction
Placebo	51/F	2	36	Myocardial infarction
Placebo+	65/M	2	82	COVID-19* and multi-organ failure
Placebo	65/M	2	69	COVID-19* (cardiac arrest)
Placebo	82/F	2	124	Dementia due to Alzheimer's
Placebo	57/F	2	80	COVID-19* (pneumonia, respiratory failure)
Placebo	66/M	2	101	Pneumonia s/p MI
Placebo	42/F	1	7	Undetermined cause of death
Placebo	53/M	2	31	Drug overdose/ respiratory arrest
Placebo	64/M	2	64	Aortic rupture
Placebo	65/M	2	75	Cardiac arrest due to bacterial pneumonia (COVID test negative)
Placebo	55/F	2	75	COVID-19 pneumonia^*
Placebo	61/F	2	15	Hemorrhagic stroke (COVID test negative)
Placebo	47/M	2	81	Cardiac arrest
Placebo	58/F	2	155	COVID-19 with septic shock*

Source: FDA generated
Total Deaths =38
* positive COVID-test
B = black W = white NH = non-Hispanic non-Latino H/L = Hispanic / Latino M = male F = female
+ subject had received one dose of Moderna Covid vaccine during the study
& on an unspecified date following a report of the subject of having "sniffles", a blood sample was positive for COVID ant bodies (~4 months after vaccination)
^ HIV population
t = Turkey sa = South Africa a = Argentina
COPD = chronic obstructive pulmonary disease

6.1.12.4 All Serious Adverse Events (SAEs)

Dose 1 through 1 month after Dose 2

SAEs were reported by 127 (0.6%) and 116 (0.5%) of participants in the BNT162b2 and placebo groups, respectively. The numbers of participants who reported at least 1 SAE were lower in the younger age group (52 [0.4%] and 49 [0.4%] for the BNT162b2 and placebo groups, respectively) than in the older age group (75 [0.8%] and 67 [0.8%] for the BNT162b2 and placebo groups, respectively). Three of the SAEs in the BNT162b2 group and none in the placebo group were assessed by the investigator as related to vaccine or vaccine administration (ventricular arrhythmia, lymphadenopathy, shoulder injury related to vaccine administration).

Reviewer Comment: Following clinical review of the adverse event narratives, two of these SAEs were considered by FDA as possibly related to vaccine: shoulder injury possibly related to vaccine administration or to the vaccine itself, and lymphadenopathy involving the axilla contralateral to the vaccine injection site. For

lymphadenopathy, the event was temporally associated and biologically plausibly related.

Deep Vein Thrombosis (DVT)
Two BNT162 recipients reported a DVT (unspecified location [n =1], leg [n =1]) 11 days after Dose 1 and 19 days after Dose 2, respectively. The first participant consequently developed a pulmonary embolism (PE). The DVT and PE resolved; the study investigator attributed the DVT to the participant's pre-existing type 1 diabetes mellitus. For the second participant, the event was ongoing at the time of the data cutoff date (March 13, 2021); the study investigator attributed the DVT to a recent ankle fracture in the same limb. No further information was provided for either participant.

Dose 1 to data cutoff date or participant's unblinding date (whichever was earlier)
SAEs were reported by 268 (1.2%) and 268 (1.2%) of participants in the BNT162b2 and placebo groups, respectively. The numbers of participants who reported at least 1 SAE were lower in the younger age group (103 [0.8%] and 117 [0.9%] for the BNT162b2 and placebo groups, respectively) than in the older age group (165 [1.8%] and 151 [1.7%] for the BNT162b2 and placebo groups, respectively). In these analyses, 58.2% of study participants had at least 4 months of follow-up after Dose 2.

Four SAEs in the BNT162b2 group and 1 in the placebo group were assessed by the investigator as related to the study intervention. Three of these SAEs in the BNT162b2 group were discussed in the subsection above (Dose 1 through 1 month after Dose 2) and the other SAE that occurred prior to unblinding was a report of paresthesia of the right leg (symptoms consistent with radicular nerve pain per the SAE narrative) occurring 47 days after Dose 2 in a participant 16-55 years of age who had other significant neurologic medical history. According to the SAE narrative, a spinal MRI obtained while the participant was symptomatic was unremarkable. A subsequent neurology evaluation and laboratories did not reveal a cause, and the symptoms resolved spontaneously. The investigator considered it a reasonable possibility that the right leg paresthesia was related to BNT162b2; however, the Applicant disagreed and stated that there was not enough evidence to establish a causal relationship apart from chronological association at the time of the report, and that was more likely that the paresthesia was associated with the participant's underlying known neurological conditions. FDA agrees with the Applicant that there is no clear basis to support a causal relationship between BNT162b2 and the SAE of paresthesia. Thus, FDA considers this SAE to be unlikely related to the vaccine.

Appendicitis
During the evaluation of safety data for the issuance of the EUA (November 2020), an imbalance was noted in the number of reported cases of appendicitis. Appendicitis was reported as a SAE for 12 participants, and numerically higher in the vaccine group: 8 vaccine participants (appendicitis [n =7], appendicitis perforated [n =1]) and 4 placebo participants (appendicitis [n =2], appendicitis perforated [n =1], complicated appendicitis [n =1]). All of the vaccine participants (n=8) and 2 placebo participants were younger than 65 years of age.

As a follow-up to this analysis, an evaluation of cases of appendicitis from Dose 1 to data end date was performed. A total of 29 (15 vaccine recipients and 14 placebo recipients) cases of appendicitis were reported and included acute, perforated and complicated cases of appendicitis. Of the 21 participants reporting appendicitis in the

16–55-year age group, 12 were in the BNT162b2 cohort/ 9 in the placebo cohort. Cases in those participants >55 years included 3 participants in the vaccine cohort and 5 in the placebo cohort. The majority of participants who experienced appendicitis were ≤65 years of age. No subject who received BNT162b2 and experienced appendicitis was older than 65 years of age.

During the placebo-controlled portion of the study, from Dose 1 to unblinding, appendicitis was reported as a SAE for 27 participants, with reports balanced between treatment groups: 14 vaccine participants (appendicitis [n =14], appendicitis perforated [n =1]) and 13 placebo participants (appendicitis [n =9], appendicitis perforated [n =1], complicated appendicitis [n =2], appendix disorder [n =1]). There were two cases of appendicitis from unblinding to the time of data cutoff (March 13, 2021): one case in the vaccine group and one case in the placebo group of perforated appendicitis.

Table 33. Analysis of Appendicitis Events, Phase 2/3, Dose 1 to Data Cutoff Date

Time to Event	BNT162b2 N=15 n (%)	Placebo N=14 n (%)	Total N=29 n (%)
Appendicitis within 7 days of Dose 1	2 (13.3%)	0 (0.0%)	2 (6.9%)
Appendicitis within 28 days of Dose 1	5 (33.3%)	0 (0.0%)	5 (33.3%)
Appendicitis within 28 days of Dose 2	3 (20.0%)	6(42.9%)	9 (31.0%)
Appendicitis within 28 days of Dose 3	0 (0.0%)	1 (7.1%)	1(7.1%)
Median number of days to event	22	50	29

Reviewer modified from OCS provided JMP clinical analysis

> *Reviewer Comment:* While the number of cases reported during blinded follow-up within 28 days after Dose 1 was 7 vs. 0 for the vaccine and placebo groups, respectively, a reverse case split (6 vs. 3) was observed within 28 days after Dose 2. Furthermore, only 1 case of appendicitis was reported within 28 days after Dose 3 (open label administration of BNT162b2 to placebo recipients who were unblinded and crossed over). Thus, there is no clear temporal pattern to suggest a causal relationship.

All cases were considered unrelated to vaccination by the study investigators and occurred no more frequently than expected in the given age groups. FDA agrees that there is no clear basis upon which to suspect that cases of appendicitis represent a vaccine-related event.

Deep Vein Thrombosis (DVT)
A total of 5 participants (2 BNT162b2 recipients, 3 placebo recipients) developed DVTs 71-115 days after study intervention Dose 2. The 2 BNT162b2 recipients both reported DVTs in the legs bilaterally with consequent PEs; all events resolved, and the causes of the DVTs are unknown. Two placebo recipients both reported DVTs in the leg, which the study investigator attributed to sport-related trauma and reduced mobility during quarantine, respectively; the event is ongoing for the first placebo recipient and resolved for the second placebo recipient. The third placebo recipient reported DVT in the arm, the cause is unknown, and the event was ongoing at the time of the data cutoff

date. No hematologic results or treatment intervention information was provided for any of the 7 participants.

The clinical features of these thromboembolic SAEs do not appear to be similar to cases of thrombosis with thrombocytopenia syndrome (TTS) observed following vaccination with adenovirus-vectored COVID-19 vaccines. During post-authorization surveillance, a safety signal for TTS has not been identified following vaccination with BNT162b2.

Myocarditis and Pericarditis
One report of pericarditis was identified in the vaccine group, occurring in a male participant >55 years of age with no medical history, 28 days after Dose 2 of vaccine; the event was assessed by the investigator as not related to the study intervention and was ongoing at the time of the data cutoff. FDA agrees with the investigator assessment. One report of myocarditis was identified in a participant 16-55 years of age in the placebo group, occurring 5 days after their second placebo dose.

Open-label follow-up: from participant unblinding to the March 13, 2021 data cutoff

Original BNT162b2 recipients
Overall, 20,309 original BNT162b2 recipients were followed after unblinding. Of these, 55 (0.3%) participants reported at least 1 SAE, 1 of which was considered related. One SAE (myocardial infarction), which occurred 71 days after Dose 2 and resolved within one day, was reported by a participant ≤55 years of age and was considered possibly related to the study intervention by the investigator. FDA disagrees with the investigator regarding the possible relatedness of an acute myocardial infarction occurring 71 days following the last vaccine dose; the long-time interval decreases the likelihood of relatedness, in our opinion. Three other participants, all of whom were >65 years of age, experienced acute myocardial infarction after unblinding, occurring at a range of 128-145 days after Dose 2; none of these events were considered related to the study intervention by the investigator and FDA agrees with those assessments.

Placebo recipients who were unblinded and received BNT162b2
Overall, 19,525 original placebo participants were unblinded and received BNT162b2. The number of participants reporting SAEs and AEs leading to withdrawal was 65/19,525 (0.03%), and 19/19,525 (0.01%), respectively. The number of participants who discontinued from the study because of related AEs was 12/19,525 (<0.01%), and 2 participants died. These AEs are discussed in more detail in Section 6.1.12.7 (Dropouts and Discontinuations) and Section 6.1.12.3 (Deaths).

Allergy to vaccine, anaphylactoid reaction, and deep vein thrombosis were reported in 1 participant each from Dose 3 to 7 days after Dose 1 of BNT162b2.

- One participant reported an AE of Grade 2 allergy to vaccine, which occurred on the day of Dose 3 vaccination, had a duration of 2 days, and resolved; this AE was assessed by the investigator as related to the study intervention. No additional information was available.
- One participant with an ongoing medical history significant for drug hypersensitivity and food and seasonal allergies reported a life-threatening SAE of anaphylactoid reaction, which occurred 2 days after Dose 3 and was resolved that same day; this SAE was assessed by the investigator as related to the study intervention (described in Section 6.1.12.5).

- One participant with a past medical history significant for deep vein thrombosis, hypertension, pulmonary arterial hypertension, right ventricular enlargement, hypercholesteremia, atherosclerosis and bilateral peripheral neuropathy reported a Grade 2 SAE of deep vein thrombosis (lower right extremity) and Grade 1 SAE of pulmonary embolism, which both occurred 2 days after Dose 3 and had both resolved with a duration of 3 days; both SAEs were assessed by the investigator as not related to the study intervention.

FDA agrees with the investigator assessments of relatedness to the study interventions listed for the three participants above.

Placebo recipients who had COVID-19 occurrence after Dose 1 and then received BNT162b2 after unblinding

A total of 852 participants originally received placebo, had protocol-confirmed COVID-19 during the blinded follow-up period, and then received BNT162b2 after unblinding. Of these, the following SAEs occurred in 3 participants:

- One participant, who was ≤55 years of age with a significant past history of a deep vein thrombosis, had a Grade 3 SAE of pulmonary embolism 6 days post Dose 4, which lasted 2 days and resolved with sequelae. The SAE was assessed as not related to the study intervention by the investigator.
- One participant, who was >55 years of age with a past medical history of hypertension, hypercholesterolemia, coronary artery disease, and a coronary artery bypass in 2006, had a Grade 3 SAE of myocardial infarction 16 days post Dose 3, which lasted 4 days and resolved with sequelae. The SAE was assessed and not related to the study intervention by the investigator.
- One participant, who was >55 years of age had 4 SAEs (none of which were assessed as related to the study intervention by the investigator):
    - 2 Grade 3 SAEs, urosepsis and acute hypoxic respiratory failure, both occurred 7 days post Dose 3, lasted 5 days, and resolved.
    - Grade 3 SAE of non-small cell lung cancer (stage III) occurred 31 days post Dose 4 and was continuing at the data cutoff date.
    - Grade 2 SAE of *Clostridium difficile* infection occurred 47 days post Dose 4 and was continuing at the data cutoff date.

FDA agrees with the investigator assessments listed for the three participants above

<u>Placebo-controlled and Open-label follow up from Dose 1 to 6 Months after Dose 2: Original BNT162b2 Participants</u>

A total of 12,006 participants originally received BNT162b2 and had at least 6 months of follow-up. SAEs were reported by 190 (1.9%) participants. The number of participants who reported at least 1 SAE was 73 (1.1%) and 117 (2.2%) in the younger and older age groups, respectively. In the first month after vaccination, 58 (0.5%) participants reported SAEs. From 1 month post Dose 2 to 6 months after Dose 2, the frequency of SAEs increased to 1.1% (n=133 participants). The following SOCs had the largest increase in SAEs (Dose 1 to 1 month after Dose 2 vs 1 month after Dose 2 to 6 months after Dose 2):

- Neoplasms, benign, malignant, and unspecified (including cysts and polyps): 4 (0.0%) vs 21 (0.2%)
- Injury, poisoning, and procedural complications: 2 (0.0%) vs 14 (0.1%)
- Infections and infestations: 14 (0.1%) vs 22 (0.2%)
- Gastrointestinal disorders: 4 (0.0%) vs 10 (0.1%)
- Respiratory, thoracic, and mediastinal disorders: 2 (0.0%) vs 8 (0.1%)

None of these SAEs were considered related to the study intervention and FDA agrees with the investigator's assessment.

No deaths or AEs leading to withdrawal were reported during the blinded and open-label follow-up periods in the group of original BNT162b2 recipients with at least 6 months of follow-up after Dose 2.

Subgroup Analyses
There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of non-fatal serious adverse events in these subgroups were generally consistent with the overall study population.

6.1.12.5 Additional Exploratory Analyses

Please refer to Sections 6.1.12.2 and 6.1.12.4 for AEs of clinical interest, by category, included among reported non-serious AEs and serious AEs, respectively.

MedDRA Queries of CDC AESIs
After a review of AEs using the CDC's list of COVID-19-related adverse events of special interest (AESI), the Applicant reported that the following terms were not reported in the study: acute disseminated encephalomyelitis, transverse myelitis, multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, encephalitis, myelitis, encephalomyelitis, meningoencephalitis, ataxia, narcolepsy, cataplexy, immune thrombocytopenia, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, Kawasaki disease, multisystem inflammatory syndrome in children (MIS-C) and in adults (MIS-A), and acute respiratory distress syndrome.

Terms that were present in the safety population are summarized below. For a given SMQ, if there was no imbalance between the BNT162b2 group versus placebo, the PTs within the SMQ were not further examined. In the case of an imbalance, the PTs /SMQs responsible for the imbalance are further described and the nature of the events characterized with regard to plausible association with vaccination.

Overall, the number and percentage of participants with any unsolicited AEs within the selected SMQs was similar in the BNT162b2 (224 [1.02%]) and placebo (217 [0.99%]) groups from Dose 1 to the unblinding date.

Table 34. Selected Standardised MedDRA Queries From Dose 1 to Unblinding Date, Blinded Placebo-controlled Follow-up Period, Phase 2/3 Participants 6 Years of Age and Older, Safety Population

SMQ/System Organ Class	BNT162b2 N=21926 n (%)	Placebo N=21921 n (%)
Participants with any unsolicited adverse events within one or more SMQs	224 (1.02)	217 (0.99)
Any unsolicited adverse events within SMQ Angioedema	30 (0.14)	29 (0.13)
Any unsolicited adverse events within SMQ Arthritis	35 (0.16)	48 (0.22)
Any unsolicited adverse events within SMQ Convulsions	2 (0.01)	2 (0.01)

SMQ/System Organ Class	BNT162b2 N=21926 n (%)	Placebo N=21921 n (%)
Any unsolicited adverse events within Demyelination (SMQ)	2 (0.01)	1 (0.00)
Any unsolicited adverse events within SOC Cardiac disorders	87 (0.4)	78 (0.4)
Any unsolicited adverse events within SMQ Hepatobiliary disorders	27 (0.1)	22 (0.1)
Any unsolicited adverse events within SMQ Hypersensitivity	182 (0.83)	161 (0.73)
Any unsolicited adverse events within SOC Skin and subcutaneous tissue disorders	134 (0.61)	119 (0.54)
Any unsolicited adverse events within Peripheral neuropathy	3 (0.01)	6 (0.03)

Source: STN 125742.0 Study C4591001-interim-mth6-report body.pdf, Section 12.2.4.4.2, adapted from Table 45, pages 281-285.
N = number of participants in the specified group.

Cardiac Disorders

Considering the observed risk of myocarditis/pericarditis, FDA analyzed adverse events within the SOC Cardiac disorders (see Appendix B) by evaluating the related narrow SMQs of Cardiac arrythmia, Ischemic heart disease and Cardiac failure. These SMQs were analyzed at 7 and 28 days after any vaccination to assess for temporal relationship. More cardiac events were reported in the older age group when compared to the younger age group, with the greatest imbalances observed in Ischemic heart disease, as expected based on age-related risk factors. A total of 16 study participants experienced cardiac events during overall blinded and unblinded follow up through March 13, 2021. Of these 16 participants, 10 vaccine recipients (8 males and 2 females) and 6 placebo recipients (4 males and 2 females) reported ischemic cardiac events and/or cardiac failure. During the first 30 days post vaccination, 5 participants in the vaccine group reported ischemic or cardiac failure events, and 2 participants in the placebo group reported myocardial infarction. Only one event occurred within 7 days of vaccination with BNT162b2. The age range was similar in both study arms (35 to 49 years in the vaccine group and 46 to 48 years in the placebo group). Individual review of these cases revealed that all subjects had at least one of the following predisposing conditions: diabetes, hyperlipidemia, and/or hypertension. No imbalances were noted between treatment groups for any of the other preferred terms within the Cardiac disorders SOC. Of note, for the 8 participants who reported 'cardiac failure congestive' at any time during follow-up, four entered into the study with this pre-existing condition (1 BNT162b2: 3 Placebo).

The occurrence of cardiac events (cardiac arrythmias, ischemic events and cardiac failure) with close temporal association to vaccination is similar between BNT162b2 and placebo groups, and any imbalances are small. Because of the small numbers of events observed, the lack of a clear temporal association, and the presence of other factors that could have explained these events, these are unlikely to be related to vaccination. There is considerable uncertainty in making a definitive causality assessment.

Hepatobiliary Disorders

An analysis of hepatobiliary-related reports demonstrated that Gallstone related disorders (SMQ) were more common in the BNT162b2 cohort when compared to

placebo (20 BNT162b2: 11 placebo). Within the BNT162b2 group, these events were more common in subjects >55 years of age (8 events reported by participants 16-55 years of age and 12 events reported by participants >55 years of age). Events occurred 3-97 days following any vaccination, with a median time to event of 19 days for the BNT162b2 group. The clinical significance of this finding of numerically higher cases of gallstone disorders is not clear.

6.1.12.6 Clinical Test Results

Clinical laboratory tests (hematology, chemistries) were assessed in Phase 1. The only common laboratory abnormality reported was transient decreases in lymphocytes 1-3 days after Dose 1, which increased in frequency with increasing dose, were mostly Grade 1-2, generally normalized at the next laboratory assessment 6-8 days after Dose 1 and did not occur after Dose 2. Among Phase 1 participants who received the 30 µg dose of BNT162b2, transient decreases in lymphocytes post-Dose 1 occurred in 5 of 12 participants 18-55 years of age and in 4 of 12 participants 65-85 years of age. These transient hematological changes were not associated with clinical symptoms.

6.1.12.7 Dropouts and/or Discontinuations

Dose 1 to data cutoff date or participant's unblinding date (whichever was earlier)
Of the 43,847 enrolled participants, 352 (1.6%) participants in the BNT162b2 group and 528 (2.4%) participants in the placebo group discontinued from the study prior to unblinding; most were due to withdrawals by the participant (n=109 [0.5%] and n=181 [0.8%], respectively), or loss to follow-up (n=151 [0.7%] and n=152 [0.7%], respectively). A total of 146 participants (n=26 [0.1%] in the BNT162b2 group and (n=120 [0.5%] in the placebo group) were discontinued because they no longer met eligibility criteria.

Dropouts due to pregnancy were balanced between the treatment groups (6 per group).

Study Withdrawal due to an AE
Of the 43,847 enrolled participants, 45 (0.21%) vaccine recipients and 51 (0.23%) placebo recipients withdrew from the study due to an AE.
Adverse events in the SOC Cardiac disorders were the most common AEs leading to withdrawal, with 10 events in the BNT162b2 group (8 of which resulted in death) and 8 in the placebo group (4 of which resulted in death):

- BNT162b2 group:
    - Did not result in death: coronary artery disease in a participant >55 years of age occurring 12 days post Dose 2, and tachycardia in a participant >55 years of age occurring 2 days post Dose 1.
    - Resulted in death: cardiac arrest in 4 participants, all >55 years of age, occurring from 31 to 117 days after vaccination, cardiac failure congestive in 1 participant 16-55 years of age occurring 69 days after Dose 2, cardio-respiratory arrest in 1 participant 16-55 years of age occurring 86 days after Dose 2, hypertensive heart disease in a participant >55 years of age occurring 71 days after Dose 2, sudden cardiac death in a participant >55 years of age occurring 42 days after Dose 2.
- placebo group:
    - Did not result in death: atrial fibrillation (participants), cardiac failure congestive, and coronary artery occlusion (1 participant each).

  - Resulted in death: myocardial infarction (2 participants each); cardiac arrest, cardiorespiratory arrest (1 participant each).

AEs in the SOC General disorders and administration site conditions were the next most common AEs leading to withdrawal (6 vaccine, 2 placebo):

- BNT162b2 groups: injection site pain in 2 participants 16-55 years of age occurring 1-2 days after Dose 1, chills and pyrexia in 1 participant >55 years of age occurring on the day of Dose 1, facial pain and swelling in 1 participant >55 years of age occurring 4 days after Dose 1, injection site dermatitis in 1 participant 16-55 years of age occurring 3 days after Dose 1, and injection site swelling in 1 participant 16-55 years of age occurring on the day of Dose 1.
- Placebo group: death and fatigue (1 participant each).

Please refer to Section 6.1.12.3 for additional details regarding deaths reported in the study.

To better characterize these study withdrawals due to AEs, an analysis of the time period from Dose 1 to 1 Month after Dose 2 was also evaluated.
Of the 43,847 enrolled participants, 32 (0.1%) participants in the BNT162b2 group and 36 (0.2%) participants in the placebo group had an AE leading to study withdrawal.
AEs in the SOC General disorders and administration site conditions were most common with 6 participants in the BNT162b2 group and 2 participants in the placebo group who withdrew from the study due to an AE:

- BNT162b2 group: injection site pain (2 participants) and chills, facial pain, injection site dermatitis, injection site swelling, pyrexia, and swelling face (1 participant each).
- placebo group: death and fatigue (1 participant each).

AEs in the SOC Cardiac disorders also occurred in 3 participants in the BNT162b2 group and 5 participants in the placebo group who withdrew from the study due to an AE:

- BNT162b2 group (1 participant each): cardiac arrest (resulted in death), coronary artery disease and tachycardia.
- placebo group: atrial fibrillation (2 participants), cardiac failure congestive, coronary artery occlusion, and myocardial infarction (1 participant each).

As noted on page 65 in Section 6.1.12.2 above, 1 vaccine recipient >55 years of age reported unilateral deafness which occurred 19 days after Dose 1 and resolved 9 days later. The participant was discontinued from study intervention and remained in the study for safety evaluation.

Open-label follow-up: from participant unblinding to the March 13, 2021 data cutoff

Placebo recipients who unblinded to receive BNT162b2
During the open-label follow-up period, most participants originally randomized in the placebo group remained in the study and received Doses 3 and 4 (88.8% and 72.4%, respectively) of BNT162b2. Overall, 19,525 original placebo participants were unblinded and received BNT162b2. The number of participants who discontinued from the study because of related AEs was 19/19,525 (0.1%). AEs in the SOC of General disorders and administration site conditions (n=7) were common, with injection site pain the most frequent (n=3), followed by chills (n=2) and fatigue (n=2).

Placebo recipients who had COVID-19 occurrence after Dose 1, then received BNT162b2 after unblinding

A total of 852 participants who originally received placebo had COVID-19 and then received BNT162b2 after unblinding. Among these, 3 participants reported AEs leading to withdrawal, all of which were assessed as related to BNT162b2:

- 1 participant with an AE of allergy to vaccine, who had a known history of asthma and allergy to arthropods, experienced the following 5 minutes after vaccine administration: facial swelling and flushing, followed by nausea and urticaria hours later; nausea resolved the same day; other symptoms resolved the next day);
- 1 participant with an AE of pain on the day of vaccination.
- 1 participant with 5 AEs (chills, injection site pain, myalgia, headache, and diarrhea) on the day of vaccination.

Original BNT162b2 Participants

Overall, 20,309 original BNT162b2 recipients, including 12,006 with at least 6 months of total follow-up, were followed after unblinding. Of these, 4 participants were withdrawn due to an AE: 1 participant reporting each of the following PTs: myocardial infarction, acute hepatic failure, injury, road traffic accident, and lung cancer with metastases to the brain. For three participants, withdrawal was due to death (myocardial infarction, road traffic accident and brain metastases). None of these events were considered related to the study intervention and FDA agrees with the assessment.

6.1.13 Study Summary and Conclusions

This randomized, blinded, placebo-controlled multinational clinical trial evaluated the safety and efficacy of BNT162b2 in >40,000 participants 16 years of age and older.

In the updated efficacy analysis, vaccine efficacy after 7 days post Dose 2 was 91.1%, (95% CI 88.8; 93.1) in participants without prior evidence of SARS-CoV-2 infection and 90.9% (95% CI: 88.5, 92.8) in the group of participants with or without prior infection. Efficacy estimates were consistently high across demographic and geographic subgroups, although interpretation of some subgroup analyses was limited by low number of cases and/or participants. Updated vaccine efficacy against severe COVID-19 occurring after 7 days after Dose 2 was 95.3% (95% CI 71.0, 99.9), with 1 case in BNT162b2 group and 21 cases in placebo group. Overall, the updated efficacy analysis results show that BNT162b2 provided high VE in preventing symptomatic COVID-19 and severe COVID-19 cases during the blinded, placebo-controlled follow-up period.

Solicited local reactions and systemic reactions after vaccination were frequent in the BNT162b2 group; these were mostly mild to moderate, generally of short duration, and more frequent in the younger age group than the older age group. The most common solicited adverse reactions, by age group, were injection site reactions (88.6% and 78.2%), fatigue (70.1% and 56.9%), headache (64.9% and 45.9%), muscle pain (45.5% and 32.5%), chills (41.5% and 24.8%), joint pain (27.5% and 21.5%), fever (17.8% and 11.5%) in the younger and older age groups, respectively. Severe adverse reactions occurred in up to 5.3% of participants, were more frequent after Dose 2 than after Dose 1 and were generally less frequent in adults ≥55 years of age as compared to younger participants.

Imbalances in unsolicited adverse events between treatment groups from Dose 1 through 1 month after Dose 2 included hypersensitivity-related adverse events (272

participants [1.1%] in the vaccine group vs. 225 participants [0.9%] in the placebo group) and lymphadenopathy (83 participants [0.4%] in the vaccine group and 7 participants [<0.1%] in the placebo group). Bell's palsy was reported by four vaccine participants and 2 placebo recipients during the blinded study period, and an additional 3 placebo/BNT162b2 recipients following unblinding, which suggests a potential causal association between vaccine and the rare occurrence of Bell's palsy. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine.

Overall, deaths and SAEs were reported by similar proportions of participants in both treatment groups. A total of 38 deaths occurred in the reporting period (19 deaths in the BNT162b2 group, 17 in placebo and 2 in the placebo/BNT162b2 group). More deaths occurred in the older age group, as expected due to increased age and comorbidities. All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate. The frequency of non-fatal serious adverse events was low (<1.2%), without meaningful imbalances between treatment groups. The number of participants who reported at least 1 SAE was higher in the older age group than in the younger age group, again as expected due to increased age and comorbidities and representing events that occur in the general population of the age groups where they occurred.

The clinical data submitted exceed FDA's expectations for data to support licensure of vaccines for prevention of COVID-19, including relevant efficacy success criteria and numbers of vaccinated study participants and follow-up time (i.e., at least 3,000 vaccinated participants in each age group with at least 6 months of total safety follow-up) for an acceptable safety database.

6.2 Study BNT162-01

NCT04380701

Title: A multi-site, Phase I/II, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults

Design
Study BNT162-01 is an ongoing Phase 1, dose-level finding study to evaluate the safety and immunogenicity of several candidate vaccines, including BNT162b2 (1, 3, 10, 20, and 30 µg), conducted in healthy German adults. The 30-µg dose level of BNT162b2 was administered to 12 adults age 18-55 years of age (inclusive) and 12 adults age 56-85 years of age (inclusive).

The primary objective was to evaluate the safety the BNT162 candidate vaccines. Secondary and exploratory objectives were to describe humoral and cellular immune responses following vaccination, measured at baseline and various time points after vaccination, specifically 7 days post Dose 2. Adverse event monitoring was the same as the safety monitoring in study C4591001.

The study started April 23, 2020. The BLA contains safety data (reactogenicity and AE analyses) up to 1 month after Dose 2 (data cutoff date: October 23, 2020), neutralizing antibody data up to ~2 months after Dose 2 (data cutoff date: October 23, 2020), and T-cell data up to ~6 months after Dose 2 (data cutoff date: March 2, 2021).

Results
Disposition of 30ug BNT162b2 group:

- Safety: Of a total of 24 participants, 12 participants 18-55 years of age 12 participants 56-85 years of age completed the visit at 1 month post-Dose 2.
- Immunogenicity: Of the 12 participants, serum neutralizing antibody and T-cell responses were available for 10 and 12 participants, respectively.

Safety: The safety profiles for adult participants 18-55 and 56-85 years of age receiving 30ug BNT162b2 in this study were similar to age-matched participants in study C4591001.

Immunogenicity: Dose-dependent increases were noted 42 days after Dose 2, compared to SARS-CoV-2 neutralizing geometric mean titers at baseline (pre-Dose 1), and most pronounced at the 30-µg dose level. The Th1 polarization of the T-helper response was characterized by the IFNγ and IL-2 production, and only minor IL-4, production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation.

Reviewer Conclusions
Immunogenicity data supported the final dose selection and prospect of benefit for the enrollment of larger numbers of participants in study C4591001. The number of participants was too small to make definitive conclusions about antibody persistence at ~6 months after Dose 2. Also, the analyses of humoral responses in this study were exploratory and not germane to the interpretation of the primary efficacy endpoint in study C4591001.

7. Integrated Overview of Efficacy

Not applicable because Study C4591001 was the only study that evaluated the efficacy of BNT612b2.

8. Integrated Overview of Safety

The number of participants who received the 30-µg dose of BNT162b2 in Study BNT162-01 (n=24) was small and would not change to the overall safety conclusions. Thus, an integrated overview of safety was not applicable.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnancy

During study C4591001 from Dose 1 through the data cutoff date of March 13, 2021, pregnancy was reported by 42 participants who received BNT162b2. For those participants who received BNT162b2 during the open-label period (originally randomized to placebo), 8 participants reported maternal exposure during pregnancy

prior to the data cutoff date. Data on Birth Outcomes, Unknown Pregnancy Outcomes and Ongoing Pregnancies is not included in the study report as the Applicant did not collect this information in their standard clinical database.

The disposition of participants 16 years of age or older who became pregnant from Dose 1 through the data cutoff date of March 13, 2021, is shown below in Table 35 (original treatment groups as randomized, N=44,047) and Table 36 (participants originally randomized to placebo who were unblinded and received BNT162b2, N=19,611). No subject in the 16–17-year-old group reported a pregnancy. One subject in the older age group (62 years of age) reported a pregnancy 139 days relative to the last dose of vaccine. Withdrawals due to pregnancy during blinded follow-up were balanced between the vaccine and placebo groups.

The known pregnancy outcomes of spontaneous abortion, miscarriages and elective abortions was similar between the vaccine and the placebo group.

Table 35. Disposition of Participants 16 Years of Age and Older Who Experienced Pregnancy, Phase 2/3 Safety Population (Data Cutoff Date March 13, 2021)

	BNT162b2[a] (N=22026) n (%)	**P**lacebo[b] **(N=22021) n (%)**	**Total** (N=44047) **n (%)**
Total number of pregnancies	42 (0.2)	47 (0.2)	89 (0.2)
Timing of pregnancy			
Completed 1 dose	5 (0.0)	8 (0.0)	13 (0.0)
Completed 2 doses	37 (0.2)	39 (0.2)	76 (0.2)
Timing of last dose relative to pregnancy			
Within 30 days of pregnancy	13 (0.1)	21 (0.1)	34 (0.1)
>30 days after pregnancy	29 (0.1)	26 (0.1)	55 (0.1)
Spontaneous Abortions	3 (0.0)	7 (0.0)	10 (0.0)
Miscarriages	3 (0.0)	5 (0.0)	8 (0.0)
Elective Abortions	0	1 (0.0)	1 (0.0)

Source: STN 125742, amendment 23, Table 1, IR Réponse, page 4-5.
Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary
[a] Includes data from Dose 1 through March 13, 2021, for participants who originally received BNT162b2.
[b] Includes data from Dose 1 to before the first dose of BNT162b2 or through March 13, 2021, for participants who originally received placebo.

Table 36. Disposition of Participants 16 Years of Age and Older Who Experienced Pregnancy and Who Had Originally Received Placebo and Then Received BNT162b2 After Unblinding, Phase 2/3 Safety Population (Data Cutoff Date March 13, 2021)

	BNT162b2[a] **(N=19611) n (%)**
Total number of pregnancies	8 (0.0)
Timing of pregnancy	
Completed 1 dose	3 (0.0)
Completed 2 doses	5 (0.0)
Timing of last dose relative to pregnancy	
Within 30 days of pregnancy	7 (0.0)
>30 days after pregnancy	1 (0.0)
Spontaneous Abortions	0 (0.0)
Miscarriages	0 (0.0)
Elective Abortions	0

Source: STN 125742, amendment 23, Table 2, IR Response, page 4-5.
Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary
[a] Includes data from first dose of BNT162b2 through March 13, 2021, for participants who originally received placebo and then received BNT162b2 after unblinding.

The data on pregnancy and pregnancy outcomes from this study is limited. As part of the postmarketing surveillance, the Applicant will perform a pregnancy registry study to assess pregnancy and infant outcomes after exposure to BNT162b2 during pregnancy among pregnant women aged 18 years or older who reside in the US or Canada. (Study C4591022). Additionally, a randomized controlled trial in pregnant women (Study C4591015) will be initiated.

Further information collected from VAERS using the terms for events related to counts for the SOCs of Pregnancy, puerperium and perinatal conditions can be found in the Pharmacovigilance Plan Review Memorandum (Division of Epidemiology).

9.1.2 Use During Lactation

It is not known if BNT162b2 is secreted in human breast milk. Data are not available to assess the effects of BNT162b2 on the breastfed infant or on milk production.

9.1.3 Pediatric Use and PREA Considerations

To address Pediatric Research Equity Act (PREA) requirements, the Applicant submitted a request for deferral of the following studies in pediatric individuals <16 years to birth, because BNT162b2 would be ready for approval for use before pediatric studies for ages 0 to <16 years are complete. The deferred studies are listed here:

- Deferred pediatric study C4591001 to evaluate the safety and effectiveness of BNT162b2 in children 12 years through 15 years of age
- Deferred pediatric study C4591007 to evaluate the safety and effectiveness of BNT162b2 in children 6 months to <12 years of age
- Deferred pediatric study C4591023 to evaluate the safety and effectiveness of BNT162b2 in infants <6 months of age

Clinical data to support the safety and effectiveness of BNT162b2 in individuals 16-17 years of age were included in this BLA.

The deferral request and pediatric plans were accepted without revisions by the Pediatric Review Committee on August 3, 2021.

9.1.4 Immunocompromised Individuals

Study C4591001 enrolled healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination and individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention were excluded from participation. Examples of conditions resulting in exclusion included but were not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjogren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1). Individuals on immunosuppressive therapy or planning on receiving

immunosuppressive therapy were not enrolled in the study. However, if there was short-term treatment with corticosteroids for an acute illness, the individual's enrollment was delayed for 28 days following the completion of that treatment. The study did enroll a small subgroup (N=200) of participants with HIV infection on stable antiretroviral therapy; these participants all had stable viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment and are discussed in more detail in Section 9.1.6 below.

Due to study exclusion criteria described above, data in the BLA submission are insufficient to inform vaccine safety and effectiveness in immunocompromised populations. Based on published reports of low antibody responses and breakthrough infections among significantly immunocompromised individuals (mainly solid organ transplant recipients) who received the two-dose vaccination series under EUA, FDA amended the EUA for the Pfizer COVID-19 Vaccine in August 2021 to allow for a third dose, at least 28 days following the second dose, in individuals at least 12 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

9.1.5 Geriatric Use

Among all participants (N=22,026) who were originally randomized to BNT162b2 in Study C4591001 and included in the safety population, 20.7% (n=4,552) were 65 years of age and older and 4.2% (n=925) were 75 years of age and older. The effectiveness in geriatric participants was consistent with that seen in younger adult participants, and no safety concerns specific to the geriatric age group were identified. The reported frequencies of adverse reactions, including myocarditis/pericarditis, are lower in the geriatric age group compared with younger adults and adolescents.

9.1.6 Patients with Human Immunodeficiency Virus (HIV) Infection

As an exploratory objective for study C4591001, the safety, immunogenicity, and efficacy of BNT162b2 vaccine was assessed in individuals with confirmed stable HIV disease (protocol amendment 6 dated September 8, 2020) in the Phase 2/3 portion of the study. Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months

A total of 200 participants ≥16 years of age, who met the prespecified criteria, were randomized 1:1 to receive BNT162b2 or placebo.

Table 37. Participants With Confirmed HIV, Phase 2/3 Safety Population

Age Group	BNT162b2 (30 mcg)	Placebo	Total
16-55 years	74	69	143
>55 years	26	31	57
Total	100	100	200

Source: STN 125742, Study C4591001, Section 14, Table 14.30 (reviewer modified), pages 357/1584.

These participants were not included in the overall Phase 3 analysis for safety or efficacy for the general population of study participants ≥16 years of age. The safety results for individuals with confirmed stable HIV disease were summarized descriptively. VE was to be assessed if there was a sufficient number of COVID-19 cases in this group of participants.

The demographics (sex, race, ethnicity and age) were similar between the BNT162b2 vaccine and placebo cohort of participants with HIV. Baseline SARS-CoV-2 status was positive for 15 participants (15%) in the BNT162b2 vaccine group and 11 participants (11%) in the placebo group. More participants in the placebo group had T-cell counts between 200-500 cells/mm3 than in the vaccine group; 28 (28.0%) compared to 16 (16.0%) respectively. Overall, the participants in the HIV subgroup were younger and more likely to be male than the general population of participants enrolled in the study. A higher percentage of participants in the HIV subgroup identified as Black or African American compared to the general study population (54.5% versus 9.5%). The median age at vaccination for the HIV subgroup was 50 years. (This mirrors what was seen in the general study population ≥16 years of age.)

Table 38. Demographic Characteristics, Blinded Placebo-controlled Follow-up Period, Phase 2/3 HIV-Positive Participants 16 Years of Age and Older, Safety Population

	BNT162b2 (30 µg) (N[a] =100) n[b] (%)	Placebo (N[a] =100) n[b] (%)	Total (N[a] =200) n[b] (%)
Sex			
Male	69 (69.0)	66 (66.0)	135 (67.5)
Female	31 (31.0)	34 (34.0)	65 (32.5)
Race			
White	44 (44.0)	37 (37.0)	81 (40.5)
Black or African American	52 (52.0)	57 (57.0)	109 (54.5)
American Indian or Alaska Native	1 (1.0)	2 (2.0)	3 (1.5)
Asian	2 (2.0)	1 (1.0)	3 (1.5)
Multiracial	1 (1.0)	2 (2.0)	3 (1.5)
Not reported	0	1 (1.0)	1 (0.5)
Ethnicity			
Hispanic/Latino	20 (20.0)	12 (12.0)	32 (16.0)
Non-Hispanic/non-Latino	80 (80.0)	87 (87.0)	167 (83.5)
Not reported	0	1 (1.0)	1 (0.5)
Country			
Argentina	3 (3.0)	1 (1.0)	4 (2.0)
Brazil	3 (3.0)	2 (2.0)	5 (2.5)
Germany	2 (2.0)	0	2 (1.0)
South Africa	27 (27.0)	27 (27.0)	54 (27.0)
Turkey	2 (2.0)	2 (2.0)	4 (2.0)
USA	63 (63.0)	68 (68.0)	131 (65.5)
Age group (at vaccination)			
16-55 Years	74 (74.0)	69 (69.0)	143 (71.5)
>55 Years	26 (26.0)	31 (31.0)	57 (28.5)
Age at vaccination (years)			
Mean (SD)	49.0 (9.74)	48.9 (11.15)	48.9 (10.44)
Median	50.0	49.0	49.5
Min, max	(22, 75)	(26, 68)	(22, 75)
Baseline SARS-CoV-2 status			
Positivec	15 (15.0)	11 (11.0)	26 (13.0)
Negatived	83 (83.0)	88 (88.0)	171 (85.5)
Missing	2 (2.0)	1 (1.0)	3 (1.5)

	BNT162b2 (30 µg) (N[a] =100) n[b] (%)	Placebo (N[a] =100) n[b] (%)	Total (N[a] =200) n[b] (%)
BMI			
Underweight (<18.5 kg/m^2)	4 (4.0)	1 (1.0)	5 (2.5)
Normal weight (≥18.5 kg/m^2 - 24.9 kg/m2)	22 (22.0)	26 (26.0)	48 (24.0)
Overweight (≥25.0 kg/m^2 - 29.9 kg/m^2)	35 (35.0)	34 (34.0)	69 (34.5)
Obese (≥30.0 kg/m2)	39 (39.0)	39 (39.0)	78 (39.0)
Cluster of differentiation 4 (CD4) count			
<200 cells/mm^3	2 (2.0)	2 (2.0)	4 (2.0)
200-500 cells/mm^3	16 (16.0)	28 (28.0)	44 (22.0)
>500 cells/mm^3	78 (78.0)	64 (64.0)	142 (71.0)
Missing	4 (4.0)	6 (6.0)	10 (5.0)
HIV ribonucleic acid (RNA)			
<50 copies/mL	93 (93.0)	96 (96.0)	189 (94.5)
≥50 copies/mL	4 (4.0)	0	4 (2.0)
Missing	3 (3.0)	4 (4.0)	7 (3.5)

Source: STN 125742, Study C4591001, Section 14, Table 14.51, pages 505-6/1584.
Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but analyzed and reported separately.
[a]. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b]. n = Number of participants with the specified characteristic.
[c]. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
[d]. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19

Solicited local reactions in participants with stable HIV disease were similar to those observed for all participants ≥16 years of age by severity, onset day, and median duration (see Table 26 and Table 27 for general population local reactions). In the subgroup of participants with stable HIV, the frequency of pain at the injection site following BNT162b2 was similar after Dose 1 compared with Dose 2 of (63.0% vs 53.3%) The frequency of redness and swelling was similar after Dose 1 compared with Dose 2 (redness: 3.7% vs 6.7%; swelling: 5.6% vs 8.3%, respectively). One (1.7%) severe reaction (pain at the injection site) was reported after Dose 2 of BNT162b2. Overall, no Grade 4 reactions were reported for either the vaccine or the placebo group. The mean duration of local reactions in those participants who received the BNT162b2 was ≤2 days.

Solicited systemic adverse reactions in participants with confirmed stable HIV disease were similar to those observed for all participants ≥16 years of age by severity, onset day, and duration Fever, headache, chills, and joint pain increased in frequency from Dose 1 to Dose 2 while fatigue, vomiting, diarrhea, and muscle pain were similar in frequency after each dose. No severe systemic events were reported after Dose 1 of BNT162b2. Following Dose 2 of BNT162b2, severe solicited systemic adverse events included 1 (1.7%) fever (>38.9°C to 40.0°C), 3 (5.0%) fatigue, 2 (3.3%) headache, 1 (1.7%) chills, and 1 (1.7%) diarrhea. No grade 4 solicited systemic adverse events were reported after either dose.

Table 39 and Table 40 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days of each dose of BNT162b2 and placebo for participants 16 years of age and older with confirmed stable HIV infection.

Table 39. Solicited Local Reactions Among HIV-Positive Participants 16 Years of Age and Older, by Maximum Severity, Within 7 Days After Each Dose, Reactogenicity Subset of the Safety Population*

	BNT162b2 Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	BNT162b2 Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Redness[c]				
Any (>2.0 cm)	2 (3.7)	3 (5.4)	4 (6.7)	1 (1.6)
Mild	2 (3.7)	1 (1.8)	3 (5.0)	1 (1.6)
Moderate	0	0	1 (1.7)	0
Severe	0	2 (3.6)	0	0
Swelling[c]				
Any (>2.0 cm)	3 (5.6)	1 (1.8)	5 (8.3)	0
Mild	2 (3.7)	0	2 (3.3)	0
Moderate	1 (1.9)	0	3 (5.0)	0
Severe	0	1 (1.8)	0	0
Pain at the injection site[d]				
Any	34 (63.0)	9 (16.1)	32 (53.3)	5 (8.1)
Mild	26 (48.1)	8 (14.3)	22 (36.7)	5 (8.1)
Moderate	8 (14.8)	1 (1.8)	9 (15.0)	0
Severe	0	0	1 (1.7)	0

Source: Modified from Table 14.72 page 546/1584
Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
No Grade 4 solicited local reactions were reported in HIV-positive participants 16 years of age and older.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
[a.] N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each reaction was the same, therefore, this information was included in the column header.
[b.] n = Number of participants with the specified reaction.
[c.] Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.
[d.] Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table 40. Solicited Systemic Reactions Among HIV-Positive Participants 16 Years of Age and Older, by Maximum Severity, Within 7 Days After Each Dose, Reactogenicity Subset of the Safety Population*

	BNT162b2 Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	BNT162b2 Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Fever				
≥38.0℃	1 (1.9)	4 (7.1)	9 (15.0)	5 (8.1)
≥38.0℃ to 38.4℃	1 (1.9)	2 (3.6)	4 (6.7)	5 (8.1)
>38.4℃ to 38.9℃	0	0	4 (6.7)	0
>38.9℃ to 40.0℃	0	2 (3.6)	1 (1.7)	0
>40.0℃	0	0	0	0
Fatigue[c]				
Any	22 (40.7)	15 (26.8)	24 (40.0)	12 (19.4)
Mild	15 (27.8)	9 (16.1)	12 (20.0)	5 (8.1)
Moderate	7 (13.0)	5 (8.9)	9 (15.0)	7 (11.3)
Severe	0	1 (1.8)	3 (5.0)	0
Headache[c]				
Any	11 (20.4)	18 (32.1)	18 (30.0)	12 (19.4)
Mild	7 (13.0)	10 (17.9)	8 (13.3)	8 (12.9)
Moderate	4 (7.4)	7 (12.5)	8 (13.3)	4 (6.5)
Severe	0	1 (1.8)	2 (3.3)	0

	BNT162b2 Dose 1 N[a] =54 n[b] (%)	Placebo Dose 1 N[a] =56 n[b] (%)	BNT162b2 Dose 2 N[a] =60 n[b] (%)	Placebo Dose 2 N[a] =62 n[b] (%)
Chills[c]				
Any	6 (11.1)	5 (8.9)	14 (23.3)	4 (6.5)
Mild	5 (9.3)	4 (7.1)	5 (8.3)	3 (4.8)
Moderate	1 (1.9)	1 (1.8)	8 (13.3)	1 (1.6)
Severe	0	0	1 (1.7)	0
Vomiting[d]				
Any	1 (1.9)	3 (5.4)	2 (3.3)	2 (3.2)
Mild	1 (1.9)	1 (1.8)	1 (1.7)	1 (1.6)
Moderate	0	0	1 (1.7)	1 (1.6)
Severe	0	2 (3.6)	0	0
Diarrhea[e]				
Any	5 (9.3)	8 (14.3)	4 (6.7)	9 (14.5)
Mild	5 (9.3)	6 (10.7)	1 (1.7)	6 (9.7)
Moderate	0	1 (1.8)	2 (3.3)	3 (4.8)
Severe	0	1 (1.8)	1 (1.7)	0
New or worsened muscle pain[c]				
Any	9 (16.7)	10 (17.9)	10 (16.7)	5 (8.1)
Mild	7 (13.0)	7 (12.5)	5 (8.3)	1 (1.6)
Moderate	2 (3.7)	3 (5.4)	5 (8.3)	4 (6.5)
Severe	0	0	0	0
New or worsened joint pain[c]				
Any	5 (9.3)	7 (12.5)	10 (16.7)	5 (8.1)
Mild	5 (9.3)	4 (7.1)	4 (6.7)	1 (1.6)
Moderate	0	3 (5.4)	6 (10.0)	4 (6.5)
Severe	0	0	0	0
Use of antipyretic or pain medication[f]	7 (13.0)	8 (14.3)	16 (26.7)	7 (11.3)

Source: Modified Table 14.79 page 587/1584
Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.
No Grade 4 solicited systemic reactions were reported in HIV-positive participants 16 years of age and older.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
[a.] N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each event or use of antipyretic or pain medication was the same, therefore, this information was included in the column header.
[b.] n = Number of participants with the specified reaction.
[c.] Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
[d.] Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
[e.] Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
[f.] Severity was not collected for use of antipyretic or pain medication.

Reviewer Comment: Regardless of the number of doses of BNT162b2 vaccine, the solicited adverse reactions and systemic adverse events observed in the stable HIV population following any dose of BNT162b2 occurred with the same or less frequency than those observed in the general study population.

Table 41 below presents the rates of adverse events reported in participants with stable HIV from dose one of vaccine or placebo until the study unblinding date. While the rate of any related AE in the stable HIV cohort was higher in the BNT162b2 group when compared to the placebo group (attributed to the overall reactogenicity of BNT162b2), rates of related severe and life-threatening events were similar between the two treatment groups.

Two participants in the vaccine group withdrew secondary to an adverse event, and 1 participant in the placebo group also withdrew from the study. Serious adverse events were similar between the two cohorts (6.6% in the vaccine group and 6.9% in the placebo group) and included one case of COVID pneumonia in the placebo group (see Table 41 below).

Table 41. Occurrence of at Least 1 Adverse Event From Dose 1 to Unblinding Date Among HIV-Positive Participants 16 Years of Age and Older, Blinded Placebo-controlled Follow-up Period, Phase 2/3 Safety Population

	BNT162b2 (N[a] =100) n=%	Placebo (N[a] =100) n=%
	n[b]	n[b]
Any event	29	15
Related[c]	19	3
Severe	2	0
Life-threatening	1	1
Any serious adverse event	2	2
Related[c]	0	0
Severe	1	0
Life-threatening	1	1
Any adverse event leading to withdrawal	2	1
Related[c]	0	0
Severe	0	0
Life-threatening	1	1
Death	1	1

Source: STN 125742, Study C4591001, Section 14, modified supplemental Table 14.118, pages 848/1584.
[a]. N = number of participants in the specified group.
[b]. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any event," n = number of participants reporting at least 1 occurrence of any event.
[c]. Assessed by the investigator as related to investigational product.

SAEs

An assessment of the HIV subgroup for the period from Dose 1 to the unblinding date shows that four participants (2 in BNT162b2 group/ 2 in placebo group) reported at least 1 SAE during the blinded, placebo-controlled follow-up period. During this same time period, 2 AEs leading to withdrawal were reported in the BNT162b2 group (1 life-threatening) and 2 AEs (life-threatening) leading to withdrawal were reported in the placebo group. These AEs are summarized in Table 42 below. Only the severe AEs of nausea, vomiting, chills, injection site pain, fever, myalgia reported by the same participant one day after Dose 2 in the BNT162b2 were thought to be related to the study product. These AEs were reported to have resolved in 3 days.

Table 42. Adverse Events That Were Severe, Serious, Life Threatening, or Led to Withdrawal, from Dose 1 to Unblinding Date, HIV-Positive Participants 16 Years of Age and Older, Blinded Placebo-Controlled Follow-up Period, Phase 2/3 Safety Population

Vaccine Group	AE Category	Dose/ Day of Onset Relative Dose	Description
BNT162b2	SAE (severe)	Dose 2 / Day 86	pneumonia
BNT162b2	SAE (life threatening)	Dose 2/ Day 74	Motor vehicle accident

Vaccine Group	AE Category	Dose/ Day of Onset Relative Dose	Description
BNT162b2	AE exposure	Dose 1 / Day 22	Pregnancy
BNT162b2	Severe AE	Dose 2/Day 1	Nausea/vomiting/chills/injection site pain /fever/ myalgia
Placebo	SAE (life-threatening)	Dose 2 / Day 72	COVID-19 pneumonia
		Dose 2/ Day 68	Diabetes mellitus
Placebo	SAE	Dose 2/ Day 71	Breast cancer

Source: FDA summary from STN 125742.0.12, Appendix 3- narratives.

- A BNT162b2 participant in the >55-year age group experienced an SAE of pneumonia 86 days after Dose 2 which lasted 8 days prior to resolution.
- A BNT162b2 participant in the >55-year age group experienced a fatal SAE of road traffic accident 73 days after Dose 2.
- A younger participant in the placebo group reported a SAE of breast cancer 71 days after Dose 2. The event is ongoing at the data cutoff date.
- A younger participant in the placebo group reported a SAE of diabetes mellitus 68 days after Dose 2, and COVID-19 pneumonia 72 days after Dose 2 which lasted 4 days and resulted in death (South Africa).

An assessment of the HIV-infected study cohort for the period from Dose 1 to the unblinding date shows that four participants (2 in BNT162b2 group/ 2 in placebo group) reported at least 1 SAE during the controlled follow-up period. During this same time period there were 2 AEs leading to withdrawal in the BNT162b2 group (1 life-threatening) and 2 AEs (life-threatening) leading to withdrawal in the placebo group.

Deaths

Two deaths were reported in participants (1 BNT162b2 and 1 placebo) with confirmed stable HIV infection:

- One female participant in the younger age group died due to COVID-19 pneumonia reported 75 days after receiving Dose 2 of placebo. This participant was diagnosed based on a local COVID-19 test that could not be confirmed as protocol-approved and was not confirmed by a test result from the central laboratory. Therefore, this participant was not included in efficacy analyses.
- One female participant in the older age group died due to a road traffic accident occurring 73 days after receiving Dose 2.

HIV-infected participants were not included in the efficacy population. A separate efficacy analysis was not performed for the HIV-infected population.

10. CONCLUSIONS

The data submitted to this BLA provide evidence to support the safety and effectiveness of BNT162b2 (30 µg), administered in two doses 3 weeks apart, for prevention of COVID-19 caused by SARS-CoV-2.

The clinical data submitted to the BLA include results of a randomized, blinded, placebo-controlled multinational clinical trial that evaluated the safety and efficacy of BNT162b2 in >40,000 participants 16 years of age and older. Overall, the updated efficacy analysis results show that BNT162b2 provided >90% VE in preventing symptomatic COVID-19, and >95% VE in preventing severe COVID-19, starting 7 days

after Dose 2. Subgroup analyses of vaccine efficacy (although limited by small numbers of cases in some subgroups) did not suggest meaningful differences in efficacy across genders, ethnic groups, geographies, or for participants with obesity or medical comorbidities associated with high risk of severe COVID-19. These findings are consistent with the VE results reported in the protocol-specified event-driven interim and final analyses that supported issuance of an EUA for this vaccine in December 2020 and provide more robust evidence of vaccine effectiveness based on a much larger number of cases observed over a longer period of placebo-controlled follow-up than was available at the time of the EUA request.

The clinical safety data submitted exceeded FDA expectations for an acceptable pre-licensure safety database of at least 3000 participants in each age group (16-55 years of age and >55 years of age) with at least 6 months of total safety follow-up. In the clinical trial, local and/or systemic solicited reactions following vaccination were generally of short duration and occurred more commonly in the BNT162b2 group than the placebo group. Severe events, when they did occur, were more common in the younger age group. Overall, deaths and SAEs were reported by similar proportions of participants in both groups. Adverse reactions other than solicited reactogenicity events identified from the clinical trial data include lymphadenopathy and potentially Bell's Palsy (the latter from a small numerical imbalance of temporally associated events). These imbalances support labeling of both lymphadenopathy and Bell's Palsy as potential adverse reactions. A slight imbalance in hypersensitivity-related events was observed during the trial, and hypersensitivity reactions reported during post-authorization use further supports inclusion of these reactions in labeling. The safety results for individuals with confirmed stable HIV disease were summarized descriptively. The proportion of subjects reporting solicited reactions in the HIV population was similar or lower than those seen in the main study population.

Post-authorization safety surveillance has identified two additional clinically important but infrequent adverse reactions: anaphylaxis and myocarditis/pericarditis. The risk of myocarditis, observed as highest in males younger than 40 years of age, is being addressed by labeling in the Warnings and Precautions Section of the US package insert, by ongoing monitoring through active and passive surveillance, and by postmarketing studies to be conducted by the Applicant, US Government agencies, and other healthcare stakeholders to further evaluate and understand these risks.

Based on the totality of data and the benefit-risk considerations as described in Section 11 below, the clinical reviewers conclude that the clinical trial data submitted in this application, and complemented by available post-authorization data and plans for post-licensure studies, support approval of BNT162b2 for the indication of active immunization to prevent symptomatic coronavirus disease 2019 (COVID 19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 43. STN125742: Risk -Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• SARS CoV-2, a novel respiratory coronavirus causing COVID-19, is currently responsible for a global pandemic that has significantly disrupted human activity on a global scale. • COVID-19 is associated with significant morbidity, mortality (>4 million deaths worldwide to date) and long-term sequelae among survivors. In the US, COVID-19 has been responsible for >2.6 million hospitalizations and >600,000 deaths to date. • While the greatest risk of severe or fatal COVID-19 is in individuals >65 years of age and those with comorbid conditions (e.g., obesity, diabetes, immunocompromising conditions), significant morbidity and mortality and long-term sequelae from COVID-19 has occurred in healthy individuals of all ages. • Individuals with asymptomatic SARS-CoV-2 infection may transmit the virus to others. • Multiple genetic variants of the virus are circulating and continue to emerge. Evidence of an increase in transmissibility, shorter incubation periods and more severe disease (e.g., increased hospitalizations or deaths) has been associated with some of these variants. • Uncertainties include: lack of complete understanding of mechanisms of pathogenesis and individual risk for severe disease; evolving epidemiology of the pandemic; and potential for emergence of SARS-CoV-2 variants with altered infectivity, virulence, and/or capacity to evade immunity from natural infection or vaccination.	• COVID-19 is a serious/life-threatening disease responsible for a globally disruptive pandemic. • Control of the COVID-19 pandemic will be necessary to return to the normal activities of pre-pandemic times. • The emergence of variants of the SARS CoV-2 virus may lead to more transmissible viruses or more severe disease. • Further research is needed to understand SARS-CoV-2 immunology, COVID-19 pathogenesis, and individual risk factors for severe disease.
Unmet Medical Need	• No therapies are currently licensed for prevention of COVID-19. Remdesivir is the only drug approved for the treatment of COVID-19, and approved use is limited to hospitalized adults and pediatric patients [12 years of age and older and weighing at least 40 kilograms (about 88 pounds)]. • Monoclonal antibodies are available under EUA for treatment and post-exposure prophylaxis but not for pre-exposure prophylaxis. • BNT162b2 is one of three COVID-19 vaccines for which an Emergency Use Authorization (EUA) has been issued. Currently, no vaccines are FDA	• Public health measures of social distancing and masking are helpful but do not prevent all transmission of the virus. • There is an unmet medical need for a FDA-approved vaccine to prevent COVID-19 caused by SARS-CoV-2. • Ongoing epidemiological and clinical surveillance is needed to inform needs related to development of pharmacologic interventions

	approved for the prevention of COVID-19, and this has been cited as a reason for vaccine hesitancy and refusal of some individuals to receive EUA vaccines. • Public health vaccination goals of immunizing 75% of the population (to achieve herd immunity) have not yet been achieved. • Non-pharmacologic measures to prevent transmission of SARS-CoV-2 include masks, social distancing, and avoidance of high-risk situations. These actions do not prevent all infections. • A recent increase in US incidence of COVID-19, following decreased incidence with the introduction of EUA vaccines, involves overwhelmingly unvaccinated individuals (especially among those with severe disease); however, this increased incidence is also associated with breakthrough cases in vaccinated individuals. • Uncertainties include whether the recent increased incidence of new infections in the US is due to waning immunity from natural infection or vaccination, to the emergence of the delta variant, or to a combination of these factors.	(including vaccines) for treatment and prevention of COVID-19 and public health recommendations for their use.
Clinical Benefit	• In the evaluable efficacy population of >40,000 participants 16 years of age and older without evidence of prior SARS-CoV-2 enrolled in an ongoing multinational, randomized placebo-controlled Phase 1/2/3 trial, vaccine efficacy against symptomatic COVID-19 during the placebo-controlled follow-up period starting from 7 days after Dose 2 was 91.1% [95%CI: 88.8;93.1]. The efficacy estimate was similar when including participants with evidence of prior SARS-CoV-2 infection, although these participants contributed only 2.7% of the total confirmed COVID-19 cases observed during placebo-controlled follow-up. • Subgroup analyses of vaccine efficacy (although limited by small numbers of cases in some subgroups) did not suggest meaningful differences in efficacy across genders, ethnic groups, geographies, and participants with obesity and medical comorbidities associated with high risk of severe COVID-19. • In the same clinical trial population of participants 16 years of age and older without evidence of prior SARS-CoV-2 infection, vaccine efficacy against severe COVID-19 during the placebo-controlled follow-up period starting from 7 days after Dose 2 was 95.3% [95% CI: 70.9%; 99.9%]. • Uncertainties in clinical benefit include: longer-term duration of protection; effectiveness in certain populations (e.g., significantly immunocompromised) not well represented in the clinical trial; effectiveness against SARS-CoV-2 variants that are antigenically or biologically different from those circulating during vaccine evaluation to date; and effectiveness against asymptomatic infection and transmissibility of the virus.	• The evidence for clinical benefit of BNT162b2 meets the evidentiary standards for approval (i.e., substantial evidence of effectiveness) for use in individuals 16 years of age and older. • Data from additional studies (post-authorization and post-approval), are needed to address uncertainties in clinical benefit.

Risk	• The most frequently reported adverse reactions in the ongoing placebo-controlled trial were solicited injection site reactions (redness, swelling, and pain) and systemic adverse reactions (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain), which were generally less frequent in older (56 years and above) vs. younger (16-55 years) participants. Solicited adverse reactions were transient, and severe adverse reactions were infrequent (~5% or less among younger participants and ~1% or less among older participants). • Among all unsolicited adverse events reported in the trial, a substantial imbalance in self-limited lymphadenopathy (87 events in vaccine recipients, mostly ipsilateral and regional to the injection site, vs. 8 events in placebo recipients) supports a causal association with the vaccine. • A total of 7 cases of temporally associated Bell's Palsy following BNT162b2 (4 cases during blinded follow-up and 3 cases during unblinded follow-up all within 9 days post-vaccination) vs. 0 such cases following placebo suggest a potential causal association. This AE was reported infrequently in the clinical trial and is being further investigated in post-authorization studies. • Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. • Post-authorization safety surveillance has identified the following additional infrequent risks plausibly associated with the vaccine: diarrhea, vomiting, severe allergic reactions including anaphylaxis and other hypersensitivity reactions, and arm pain ipsilateral to the injection site. • Extensive clinical and nonclinical experience has yielded no evidence of vaccine-enhanced disease (or more severe COVID-19 as a marker for vaccine-enhanced disease) following vaccination with BNT162b2. • Uncertainties related to risks of myocarditis and pericarditis include lack of precise estimates for excess risk across various age and gender subgroups, including whether and how frequently subclinical cases occur, and longer-term outcomes and prognoses. • Other uncertainties related to risks in general include: more robust characterization of the safety profile through active safety surveillance and/or controlled observational studies in specific populations (e.g., individuals with prior COVID-19, pregnant women, and significantly immunocompromised	• The most commonly manifested risks are mild to moderate, self-limited injection site and systemic adverse reactions. • Less commonly manifested but potentially serious risks include severe allergic reactions and myocarditis/pericarditis. Additional data are needed to better quantify the risks of myocarditis and pericarditis and to understand long-term prognoses for vaccine-associated myocarditis and pericarditis. • Although the potential for vaccine enhanced disease has been evaluated throughout vaccine development and post-authorization use, this theoretical risk is not substantiated by the totality of evidence from nonclinical studies, clinical trials, and post-authorization COVID-19 case surveillance and observational studies.

	individuals); and whether additional rare adverse reactions could be identified with increased exposure and longer follow up.	
Risk Management	• Labeling for COMINRATY describes the common and uncommon (but potentially serious) risks associated with the vaccine. The labeling includes warning statements for severe allergic reactions and myocarditis/pericarditis. • The Applicant will be required to conduct post-approval studies to further evaluate vaccine safety and effectiveness, and specifically to better understand the identified risks of vaccine-associated myocarditis and pericarditis and their long-term sequelae.	• Risk mitigation strategies for BNT162b2 for use in individuals 16 years of age and older include communication of risks and benefits through labeling, directed counseling prior to vaccination according to individual risks and benefits, and a pharmacovigilance plan to further evaluate risks. • Ongoing monitoring of COVID-19 epidemiology (including emergence of variants) and vaccine effectiveness will also be critical to updating benefit risk assessments and risk mitigation strategies as the pandemic evolves over time.

11.2 Risk-Benefit Summary and Assessment

COVID-19 caused by SARS-CoV-2 is associated with a wide spectrum of manifestations, including mild illness in some individuals but severe morbidity (in some cases with long-term sequelae) and/or mortality in others. Over 4 million deaths attributable to COVID-19 have been reported worldwide since the beginning of the pandemic in late 2019, with >600,000 US deaths since the beginning of the pandemic and >2.6 million US hospitalizations during the year starting in August 2020 and ending in August 2021. Currently, the US is experiencing its third surge of COVID-19, associated with widespread transmission of the SARS-CoV-2 delta variant nationally. While the greatest risk of severe or fatal COVID-19 is in individuals >65 years of age and those with comorbid conditions (e.g., obesity, diabetes, immunocompromising conditions), significant morbidity and mortality and long-term sequelae from COVID-19 has occurred in healthy individuals of all ages. In addition to individual-level morbidity and mortality, the COVID-19 pandemic has overwhelmed healthcare systems during periods of high incidence, and the effects of SARS-CoV-2 infection, COVID-19 disease, and the necessary public health measures implemented to prevent infection and illness have severely disrupted human activities on a global scale. While three COVID-19 vaccines have received emergency use authorization in the US based on having met applicable statutory criteria, including authorization of BNT162b2 for use in individuals 12 years of age and older, full approval of a COVID-19 vaccine that has met the FDA evidentiary standard for safety, effectiveness, and manufacturing quality and consistency would represent an important step in addressing the unmet need for approved pharmacologic interventions for prevention of COVID-19.

A randomized, blinded, multinational placebo-controlled trial (C4591001) that enrolled >40,000 participants 16 years of age and older demonstrated the clinical benefit of BNT162b2 in preventing PCR-confirmed COVID-19 of any severity during the trial's blinded, placebo-controlled follow-up period, with an estimated vaccine efficacy of >90% from 7 days after completion of the 2-dose vaccination regimen. Subgroup analyses of vaccine efficacy (although limited by small numbers of cases in some subgroups) did not suggest meaningful differences in efficacy across genders, ethnic groups, geographies, or for participants with medical comorbidities associated with high risk of severe COVID-19. Data from numerous published observational studies of real-world use of the vaccine, although not independently reviewed and confirmed by FDA, appear to corroborate the high level of protection observed in the clinical trial, including against COVID-19 associated hospitalization and death, across various patient populations and geographic regions. Although some more recently published observational studies that evaluated vaccine effectiveness during emergence of the delta variant appear to suggest decreased protection against less severe COVID-19 caused by this variant, protection against hospitalization and death appears stable at this time. Remaining uncertainties regarding the clinical benefits of BNT162b2 in individuals 16 years and older include its level of protection against asymptomatic infection and transmission of SARS-CoV-2, including for the delta variant, durability of protection beyond 6-8 months (the current limit of observation in the clinical trial and observational studies), confirmation of more robust estimates of effectiveness in certain populations not well represented in the clinical trial (including individuals with prior SARS-CoV-2 infection), and vaccine effectiveness against future emerging variants.

Risks demonstrated to be associated with use of BNT162b2 in individuals 16 years of age and older include common self-limited local and systemic adverse reactions characterized in the clinical trial, which are mostly mild to moderate but can be severe in some individuals (~5% or fewer, depending on the adverse reaction), and two rare but clinically important serious adverse reactions detected through post-authorization safety surveillance: anaphylaxis and myocarditis/pericarditis. The crude reporting rate for anaphylaxis in VAERS through July 2021 (which includes unconfirmed and potentially duplicate reports) has been ~6 cases per million doses, which is similar in magnitude to rates of anaphylaxis reported for other preventive vaccines. Reporting rates for medical chart-confirmed myocarditis/pericarditis in VAERS have been higher among males under 40 years of age than among females and older males and have been highest in males 12-17 years of age (~65 cases per million doses as per CDC communication on August 20, 2021). Although some cases of vaccine-associated myocarditis/pericarditis required intensive care support (with several suspected fatal cases under CDC investigation but not confirmed at the time of this review), available data from short-term follow-up suggest that most individuals affected by vaccine-associated myocarditis/pericarditis have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals, and additional uncertainties regarding the risk of myocarditis/pericarditis include: whether and to what extent subclinical cases might occur, and if they do what are the long-term outcomes; the mechanism of pathogenesis; and individual factors conferring increased risk for vaccine-associated myocarditis/pericarditis. Other risk uncertainties for BNT162b2 in general include: more robust characterization of the safety profile through active safety surveillance and/or controlled observational studies in specific populations (e.g., individuals with prior COVID-19, pregnant women, and significantly immunocompromised individuals); and whether additional rare but clinically important adverse reactions could be identified with increased exposure and longer follow up.

Since vaccine-associated myocarditis/pericarditis is the most clinically significant identified risk, FDA undertook a quantitative benefit-risk assessment to model the excess risk of myocarditis/pericarditis vs. the expected benefits of preventing COVID-19 and associated hospitalizations, ICU admissions, and deaths (summarized in Section 4.7 of this review memo, with more details provided in the review memo from the CBER Analytics and Benefit-Risk Assessment Team). For estimation of risk, the model took a conservative approach by relying on non-chart-confirmed cases from a US healthcare claims database (OPTUM) that could provide a control group and greater confidence in denominators for vaccine exposures. Thus, the estimates of excess risk in this model are higher than the rates estimated from reports to VAERS (an uncontrolled passive surveillance system), with an age/sex-stratified estimated excess risk approaching 200 cases per million vaccinated males 16-17 years of age (the age/sex-stratified group with the highest risk). For estimation of benefit, the model output was highly dependent on the assumed COVID-19 incidence, as well as assumptions about vaccine efficacy and duration of protection. The assessment therefore considered a range of scenarios including but not limited to: a “most likely” scenario with incidence rates reflecting the recent delta variant surge and assumption of diminished vaccine effectiveness (70% overall, 80% against COVID-19 hospitalization) compared to that observed in the clinical trial; and a “worst-case” scenario with low COVID-19 incidence reflecting the July 2021 nadir and the same somewhat diminished vaccine effectiveness as in the “most likely” scenario.

For males and females 18 years of age and older and for females 16-17 years of age, even before accounting for morbidity prevented from non-hospitalized COVID-19, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under all conditions examined. For males 16-17 years of age, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under the "most likely" scenario, but that predicted excess cases of vaccine-associated myocarditis/pericarditis would exceed COVID-19 hospitalizations, ICU admissions and deaths under the "worst case" scenario. However, this predicted numerical imbalance does not account for the greater severity and length of hospitalization, on average, for COVID-19 compared with vaccine-associated myocarditis/pericarditis. Additionally, the "worst case" scenario model predicts prevention of >13,000 cases of non-hospitalized COVID-19 per million vaccinated males 16-17 years of age, which would include prevention of clinically significant morbidity and/or long-term sequelae associated with some of these cases. Finally, the model does not account for indirect societal/public health benefits of vaccination. Considering these additional factors, FDA concluded that even under the "worst case" scenario the benefits of vaccination sufficiently outweigh risks to support approval of the vaccine in males 16-17 years of age.

Uncertainties in the quantitative benefit-risk assessment include those around estimates of excess risk from vaccine-associated myocarditis/pericarditis and those around predicting future COVID-19 incidence and vaccine effectiveness with potential emergence of new SARS-CoV-2 variants. It is possible that the benefit-risk balance could become less favorable than predicted by the model, in particular for males 16-17 years of age, if sustained dramatic decreases in COVID-19 incidence occur, if additional information about vaccine-associated myocarditis/pericarditis demonstrates much higher rates and/or worse outcomes than currently appreciated, or if vaccine efficacy against circulating variants diminishes substantially. However, currently available data support a benefit-risk balance that is clearly favorable for approving BNT162b2 for use in all individuals 16 years of age and older. Mitigation of the observed risks and associated uncertainties will be accomplished through labeling (including warning statements regarding risks of allergic reactions and vaccine-associated myocarditis/pericarditis) and through continued safety surveillance and postmarketing studies (as summarized in Section 11.6) to further assess and understand these risks.

11.3 Discussion of Regulatory Options

The BNT162b2 vaccine is currently available under EUA for use in individuals 12 years of age and older. The Applicant has requested, and the data support, approval of BNT162b2 (trade name COMIRNATY following approval) for use in individuals 16 years of age and older to prevent COVID-19 caused by SARS-CoV-2. At this time, the Applicant has not yet requested approval of the vaccine for use in adolescents 12-15 years of age because additional safety data, including longer-term follow-up and further characterization of the risk of myocarditis/pericarditis in this age group, are needed to inform a benefit-risk assessment and to meet the evidentiary standard to support approval. As available evidence continues to meet the statutory criteria for EUA (including that available evidence supports the known and potential benefits outweigh the known and potential risks) for adolescents 12-15 years of age, the vaccine will

remain available under EUA for use in this age group following its full approval for use in individuals 16 years of age and older.

11.4 Recommendations on Regulatory Actions

The clinical reviewers recommend approval of BNT162b2 for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

11.5 Labeling Review and Recommendations

The package insert was submitted in the format required by FDA's Final Rule titled "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling", referred to as the "Pregnancy and Lactation Labeling Rule (PLLR)" effective June 30, 2015. Communications between the Applicant and CBER resulted in revisions to the original prescribing information which reflects the data submitted in support of the application for licensure. Of note is the addition to the WARNINGS AND PRECAUTIONS section to describe the occurrence of myocarditis and pericarditis in subjects who receive BNT162b2 and the increase risk observed for adolescents and young adult males.

The data within the label was found to be consistent with and supported by the information and data in the BLA application.

11.6 Recommendations on Postmarketing Actions

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).
FDA has determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of myocarditis and pericarditis and identify an unexpected serious risk of subclinical myocarditis.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks.
Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies to include:

Postmarketing requirement (PMR) safety studies under section 505(o) of the Federal Food, Drug, and Cosmetic Act to assess the known serious risks of myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis:

1. Study C4591009, entitled "A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY
2. Study C4591021, entitled "Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

3. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY.
4. Study C4591036 a prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network).
5. A prospective assessment of the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age enrolled in Study C4591007.
6. Study C4591031 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a third dose of COMIRNATY in a subset of participants 16-30 years of age.

Postmarketing commitment (PMC) safety studies agreed upon by FDA and Applicant:

1. Study C4591022, entitled “Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post- Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists/MotherToBaby Pregnancy Registry.”
2. Study C4591012, entitled “Post-emergency Use Authorization Active Safety Surveillance Study Among Individuals in the Veteran’s Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine.”

Voluntary postmarketing studies: The Applicant has agreed to provide updates regarding post-EUA studies that continue as voluntary studies post-licensure in periodic safety update reports (PSURs).

1. C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 vaccine in the U.S. Department of Defense population following Emergency Use Authorization
2. C4591008: HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 Vaccine in U.S. healthcare workers, their families, and their communities

At this time, the available safety data do not suggest a safety concern that would require a Risk Evaluation and Mitigation Strategy.

APPENDIX A CHARLSON COMORBIDITY INDEX

This index is based on a list of 19 conditions identified from diagnoses in hospital and physician data. Each condition is assigned a weight from 1 to 6. The index score is the sum of the weights for all identified conditions (Charlson et al., 1987). An index score of 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity.

Charlson Index Diagnoses: Cancer, Chronic Pulmonary Disease, Diabetes without Complications, Congestive Heart Failure, Cerebrovascular Disease, Dementia, Renal Disease, Peripheral Vascular Disease, Myocardial Infarction, Diabetes with Complications, Paraplegia and Hemiplegia, Connective Tissue Disease-Rheumatic Disease, Peptic Ulcer Disease, Mild Liver Disease, Metastatic Carcinoma, Moderate or Severe Liver Disease, /AIDS.

Reference: Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373– 383. [PubMed: 3558716]

APPENDIX B CARDIAC DISORDERS FROM DOSE 1 TO DATE OF UNBLINDING AMONG PHASE 2/3 PARTICIPANTS 16 YEARS OF AGE AND OLDER

Table 44. Cardiac Disorders, by System Organ Class and Age Group, From Dose 1 to Unblinding Date, Phase 2/3 Subjects 16 Years of Age and Older, Safety Population

	16-55 Years of Age				>55 Years of Age				Total			
	BNT162b1		Placebo		BNT162b1		Placebo		BNT162b1		Placebo	
System Organ Class	N=12995		N=13026		N=8931		N=8895		N=21926		N=21921	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac disorders (SOC)	30	(0.2)	31	(0.2)	57	(0.6)	47	(0.5)	87	(0.4)	78	(0.4)
Tachycardia	10	(0.1)	4	(0.0)	5	(0.1)	3	(0.0)	15	(0.1)	7	(0.0)
Atrial fibrillation	2	(0.0)	3	(0.0)	11	(0.1)	14	(0.2)	13	(0.1)	17	(0.1)
Palpitations	3	(0.0)	13	(0.1)	4	(0.0)	3	(0.0)	7	(0.0)	16	(0.1)
Acute myocardial infarction	2	(0.0)	1	(0.0)	4	(0.0)	3	(0.0)	6	(0.0)	4	(0.0)
Cardiac arrest	0	(0.0)	0	(0.0)	6	(0.1)	2	(0.0)	6	(0.0)	2	(0.0)
Coronary artery disease	1	(0.0)	1	(0.0)	5	(0.1)	5	(0.1)	6	(0.0)	6	(0.0)
Angina pectoris	1	(0.0)	0	(0.0)	4	(0.0)	1	(0.0)	5	(0.0)	1	(0.0)
Cardiac failure congestive	1	(0.0)	0	(0.0)	4	(0.0)	3	(0.0)	5	(0.0)	3	(0.0)
Myocardial infarction	0	(0.0)	4	(0.0)	4	(0.0)	4	(0.0)	4	(0.0)	8	(0.0)
Bradycardia	1	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)	3	(0.0)	2	(0.0)
Angina unstable	1	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)	2	(0.0)	3	(0.0)
Left ventricular hypertrophy	0	(0.0)	1	(0.0)	2	(0.0)	0	(0.0)	2	(0.0)	1	(0.0)
Myocardial ischaemia	1	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)	0	(0.0)
Ventricular extrasystoles	0	(0.0)	0	(0.0)	2	(0.0)	0	(0.0)	2	(0.0)	0	(0.0)
Ventricular tachycardia	1	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)	0	(0.0)
Acute coronary syndrome	1	(0.0)	2	(0.0)	0	(0.0)	2	(0.0)	1	(0.0)	4	(0.0)
Acute left ventricular failure	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Arrhythmia	0	(0.0)	1	(0.0)	1	(0.0)	2	(0.0)	1	(0.0)	3	(0.0)
Arrhythmia supraventricular	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Arteriospasm coronary	1	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Atrioventricular block complete	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)	1	(0.0)	1	(0.0)
Atrioventricular block first degree	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Bundle branch block right	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)

System Organ Class Preferred Term	16-55 Years of Age BNT162b1 N=12995		16-55 Years of Age Placebo N=13026		>55 Years of Age BNT162b1 N=8931		>55 Years of Age Placebo N=8895		Total BNT162b1 N=21926		Total Placebo N=21921	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac disorder	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Cardio-respiratory arrest	1	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Cardiomegaly	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Cardiovascular disorder	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Coronary artery dissection	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Hypertensive heart disease	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Left ventricular dysfunction	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Mitral valve incompetence	0	(0.0)	2	(0.0)	1	(0.0)	1	(0.0)	1	(0.0)	3	(0.0)
Mitral valve prolapse	0	(0.0)	1	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Pericarditis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Sinus tachycardia	1	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Supraventricular tachycardia	1	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)	1	(0.0)
Tricuspid valve incompetence	0	(0.0)	1	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Ventricular arrhythmia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Aortic valve incompetence	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	0	(0.0)	2	(0.0)
Arteriosclerosis coronary artery	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Atrial flutter	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Bundle branch block left	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Cardiac failure acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Coronary artery occlusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Junctional ectopic tachycardia	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Left atrial enlargement	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myocarditis	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pericardial effusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Postural orthostatic tachycardia syndrome	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Sinus bradycardia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Tachyarrhythmia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)

Source: OCS Analysis Studio, Safety Explorer.
Demographic Filters: TRT01A = "BNT162b2 Phase 2/3" or "Placebo", AGEGR1 = "16-55 Years" or ">55 Years"; SAF1FL = "Y"
Adverse Event Filters: VPHASE = "Vaccination 1" or "Vaccination 2" or "Follow Up 1" or "Follow Up 2", AEBODSYS = "CARDIAC DISORDERS"

APPENDIX C DEATH NARRATIVES

Narratives for COVID-19-related deaths

- 80-year-old white, non-Hispanic male who received two doses of BNT162b2 ((b) (6) and (b) (6)). Pertinent medical history includes systolic congestive heart failure (since 2016); hypertension, hyperlipidemia, gastroesophageal reflux disease, and atrial fibrillation (April 2018); hypokalemia (since July 2018); neuropathy and chronic back pain (both since August 2019); and cerebrovascular accident (on (b) (6)). Subject was transported to ER with garbled speech, increased confusion, shortness of breath and chest congestion. As part of the medical work-up a SARS-CoV-2 test was performed which was positive. The subject was diagnosed with COVID-19 pneumonia on (b) (6) days after receiving Dose 2. The subject died of COVID-19 pneumonia on (b) (6), ((b) (6) days after receiving Dose 2).

- 68-year-old black/ African American female with a pertinent medical history thyroid cancer and thyroidectomy (both in 1982), hyperlipidemia (since 2010), hypertension (since 2013), emphysema (since 2017), and malignant lung neoplasm (in 2017), received Placebo Dose 1 on (b) (6) and Placebo Dose 2 on (b) (6) (Day 22). Two separate COVID-19 tests were reported as positive prior to hospital admission. The subject was diagnosed with acute respiratory failure and COVID-19 on (b) (6) days after receiving Dose 2, and died of the events on (b) (6) days after receiving Dose 2.

- 65-year-old white male with a pertinent medical history of hyperlipidemia and hypertension (since 2010) and pulmonary fibrosis (since 2014), received Placebo Dose 1 on (b) (6) and Placebo Dose 2 on (b) (6) (Day 22). On (b) (6) (Day 85), it was noted that the subject received a prohibited vaccination (Moderna COVID-19 vaccine [mRNA-1273]) through his employer during the study period. The subject was diagnosed with COVID-19 infection leading to multiple organ dysfunction syndrome on (b) (6) days after receiving Placebo Dose 2. The subject experienced shortness of breath, fever, cough, fatigue, and muscle aches “a day or so after” exposure to COVID-19 on December 28, 2020 (Day 90). On (b) (6) (Day (b) (6)), the subject received monoclonal antibodies from his primary care physician but later that day presented to the emergency department with weakness, dyspnea, nausea, and diarrhea and was subsequently hospitalized with COVID-19 (Positive SARS-CoV-2 test). The subject died from COVID-19 and multiorgan failure on (b) (6) (~(b) (6) days after the second vaccination).

- 65-year-old white male with a pertinent medical history of coronary artery disease (since 1983); hypercholesterolemia and hypertension (both since 2010); and dyspepsia (since 2012), and obesity. Subject received placebo Dose 1 on (b) (6) and placebo Dose 2 on (b) (6) (Day 24). The subject was diagnosed with COVID-19 by self-swab and local testing (December 1, 2020). The subject died of COVID-19 complicated by cardiac arrest on (b) (6) days after receiving Dose 2.

- 57-year-old white female (Hispanic/Latino) with a pertinent medical history of type 2 diabetes mellitus (since 1995); hypothyroidism and asthma (both since 2005);

hypercholesterolemia (since 2010); vitamin D deficiency (since Jan 2020); and insomnia and sleep apnea (both since May 2020), received placebo Dose 1 on (b) (6) and placebo Dose 2 on (b) (6) (Day 22). The subject developed COVID-19 infection (SARS-CoV-2 nucleic acid amplification test was positive) and pneumonia on November 26, 2020, 58 days after receiving Dose 2; and acute hypoxemic respiratory failure on November 28, 2020, 60 days after receiving Dose 2. The subject died of the COVID-19 infection, pneumonia, and acute hypoxemic respiratory failure on (b) (6) days after receiving Dose 2.

- 55-year-old black South African female with a pertinent medical history of asthma (since 1997), (b) (6) infection (since 2008), and hypertension and obesity (both since 2010), received placebo Dose 1 on (b) (6) and placebo Dose 2 on (b) (6) (Day 22). The subject was diagnosed with diabetes mellitus on December 28, 2020, 68 days after receiving Dose 2. On January 1, 2021, the subject was diagnosed with COVID-19 pneumonia (SARS-CoV-2 PCR positive), 72 days after receiving Dose 2. The subject died of COVID-19 pneumonia on (b) (6) days after receiving Dose 2.

- 58-year-old white Hispanic/Latino female (Argentina) received placebo Dose 1 on (b) (6) and placebo Dose 2 on (b) (6) (Day 21). SARS-CoV-2 NAAT result at the time of the COVID-19 illness on December 26, 2020 (Day 120) was positive. On (b) (6) (Day (b) (6)), she died because of septic shock in the context of a severe COVID-19 illness.