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

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

6.1.11.5 Exploratory and Post Hoc Analyses

Not Applicable.

6.1.12 Safety Analyses

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

7. Integrated Overview of Efficacy

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

8. Integrated Overview of Safety

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

9. Additional Statistical Issues

Not Applicable.

10. Conclusions

10.1 Statistical Issues and Collective Evidence

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

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

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

10.2 Conclusions and Recommendations

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

Application Type	Original BLA
STN	125742/0
CBER Received Date	May 18, 2021
PDUFA Goal Date	January 16, 2022
Division / Office	OVRR
Committee Chair	Ramachandra Naik
Product Reviewer	Xiao Wang
Project Manager	Mike Smith and Laura Gottschalk
Priority Review	Yes
Reviewer Name	Xinyu Tang
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Concurring Reviewer, VEB, DB, OBE
	Tsai-Lien Lin, Branch Chief, VEB, DB, OBE
	John A. Scott, Director, DB, OBE
Applicant	BioNTech Manufacturing GmbH in partnership with Pfizer, Inc.
Established Name	COVID-19 Vaccine, mRNA
Trade Name	COMIRNATY®
Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc.	After preparation, each 0.3 mL dose contains 30 µg modified mRNA encoding SARS-CoV-2 spike glycoprotein
Dosage Form and Route of Administration	Injectable Suspension, Intramuscular
Dosing Regimen	Two 0.3 mL doses, 3 weeks apart
Indication and Intended Population	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older

Table of Contents

Glossary 3

1. Executive Summary 3

2. Regulatory Background 4

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

4. Review of the Method Validation of the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay 5

- 4.1 Introduction 5
- 4.2 Experimental Design 6
- 4.3 Statistical Analysis 7
- 4.4 [redacted] Linearity 7
- 4.4 Precision 9
- 4.5 Limits of Quantitation 10
- 4.6 Assay Intermediate Precision 10
- 4.7 Limit of Detection 11
- 4.8 Extravariability of Replicates 11

5. Review of the Report for Co-validation of Test Method TM100010380 - Determination of the [redacted] of PF-07302048 (BNT162b2 Construct, Drug Product) by [redacted] 11

- 5.1 Introduction 11
- 5.2 Validation Outline 12
- 5.3 Precision – Repeatability 13
- 5.4 Precision – Reproducibility 14
- 5.5 Specificity 15
- 5.6 Detection Limit 15
- 5.7 Robustness 17

6. Conclusions 17

GLOSSARY

BLA	biologics license application
CI	confidence interval
COVID-19	Coronavirus Disease 2019
DL	detection limit
dLIA	direct Luminex assay
DP	drug product
DPC	drug product control
DS	drug substance
GMT	geometric mean titer
IR	information request
LLOQ	lower limit of quantitation
IM	intramuscular
IND	Investigational New Drug application
LNP	lipid nanoparticle
LOD	limit of detection
[redacted]	[redacted]
mRNA	messenger RNA
[redacted]	[redacted]
RSD	relative standard deviation
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SARS-CoV-2 mNG NT	SARS-CoV-2 mNeonGreen virus microneutralization assay
S/N	signal-to-noise
TDV	Titer Determining Value
ULOQ	upper limit of quantitation
VCA	variance components analysis

1. Executive Summary

BioNTech and Pfizer submitted an original Biologics License Application (BLA) on May 18, 2021 for BNT162b2. BNT162b2 is a prophylactic vaccine that prevents Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The proposed indication is active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥16 years of age. The proposed dosage is 30 µg via intramuscular (IM) injection following a dosing regimen of two 0.3-mL doses given three weeks apart.

This review memo focuses on the statistical review of the non-clinical aspects of this submission, including the validation of the clinical immunogenicity assay as well as the in-vitro potency assay. Specifically, this review memo covers:

- the validation of the SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT) for the detection of serum antibodies capable of neutralizing SARS-CoV-2 (VR-MVR-10083), and
- the validation of Test Method TM100010380 v5.0 for determination of the [redacted] of PF-07302048 (BNT162b2 construct, Drug Product) by [redacted] (VAL100147509)

based on the validation reports submitted in Module 5.3.1.4 of BLA125742/0.0 and Module 3.2.R of BLA125741/0.19, which have not been reviewed previously.

With respect to the validation of the SARS-CoV-2 mNG NT assay, results from the validation study suggest acceptable accuracy and precision. The limit of detection (LOD), lower limit of quantitation (LLOQ), and upper limit of quantitation (ULOQ) were determined to be [redacted], respectively. The LOD study demonstrated an acceptable false positive rate but did not evaluate the false negative rate at the LOD. Because this assay was not used in the determination of serostatus in clinical studies included in this BLA submission, the unknown false negative rate does not impact the approval of this BLA. However, the false negative rate may be a concern in the future, depending on future use of this assay.

With respect to the validation of Test Method TM100010380 v5.0 (referred to as the [redacted] assay hereafter), results from the validation study suggest acceptable specificity and robustness to [redacted]. The detection limit (DL) was determined to be [redacted]. The repeatability and reproducibility of the assay were estimated to be [redacted] relative standard deviation (RSD), respectively. Since the [redacted] assay was validated as a limit test, the repeatability and reproducibility results were evaluated for information only.

In conclusion, I consider both the SARS-CoV-2 mNG NT and [redacted] assays adequate for their intended uses in support of this BLA.

2. Regulatory Background

The Investigational New Drug Application (IND19736) for BNT162b2 was submitted on April 29, 2020. Fast Track Designation was granted on July 7, 2020 for individuals 18 years of age and older. On December 11, 2020, Emergency Use Authorization (EUA 27034) of BNT162b2 for active immunization to prevent COVID-19 in individuals 16 years of age and older was granted (EUA product identified as Pfizer-BioNTech COVID-19 Vaccine). BioNTech and Pfizer submitted this BLA on May 18, 2021 for BNT162b2.

The following documents regarding clinical assays were submitted in Module 5.3.1.4 of BLA125741/0.0:

- Report on Method Validation of a Cepheid Xpert® Xpress PCR Assay to Detect SARS-CoV-2 (VR-MVR-10080, Version 3.0),
- Method Validation Report for the Elecsys Anti-SARS-CoV-2 Assay (VR-MVR-10081, Version 2.0),
- Qualification Report for a [redacted] Direct Luminex Assay (dLIA) for Quantitation of IgG Antibodies to SARS-CoV-2 S1 Protein in Human Sera (VR-MQR-10211, Version 2.0),
- Qualification Report for a [redacted] Direct Luminex Assay (dLIA) for Quantitation of IgG Antibodies to SARS-CoV-2 RBD Protein in Human Sera (VR-MQR-10212, Version 2.0),

- Qualification of the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay (VR-MQR-10214, Version 2.0), and
- Method Validation of the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay (VR-MVR-10083, Version 1.0).

All these qualification and validation reports have been reviewed during the IND stage, except for the validation report for the SARS-CoV-2 mNG NT assay, which is covered in this review memo.

The following document regarding the potency assay was submitted in Module 3.2.R of BLA125741/0.19:

- Report for Co-Validation of Test Method TM100010380 – Determination of the [redacted] of PF-07302048 (BNT162b2 Construct, Drug Product) by [redacted] (VAL100147509, Version 1.0).

This validation report has not been previously reviewed during the IND stage and is covered in this review memo as well.

3. Sources of Data and Other Information Considered in the Review

The following documents submitted to the BLA are reviewed:

- Method Validation of the SARS-CoV-2 mNeonGreen virus microneutralization assay used for the detection of serum antibodies capable of neutralizing SARS-CoV-2 (VR-MVR-10083, Version 1.0) (BLA125742/0.0, dated February 9, 2021, received May 6, 2021),
- Report for Co-Validation of Test Method TM100010380 – Determination of the [redacted] of PF-07302048 (BNT162b2 Construct, Drug Product) by [redacted] (VAL100147509, Version 1.0) (BLA125742/0.19, Module 3.2.R, dated July 16, 2021, received July 28, 2021).
- Response to 04 Aug 2021 FDA Information Request (IR) (BLA125742/0.34, Module 1.11.1, dated August 6, 2021, received August 6, 2021), and
- Validation of Analytical Procedure – [redacted] (BLA125742/0.34, Module 3.2.P.5.3, dated August 6, 2021, received August 6, 2021).

The following document submitted to the IND is also referred to when reviewing the validation of the SARS-CoV-2 mNG NT assay:

- Validation Protocol for the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay (VR-MVP-10074, Version 2.0) (IND19736/157, Module 5.3.1.4, dated December 2, 2020, received December 4, 2020).

4. Review of the Method Validation of the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay

4.1 Introduction

The SARS-CoV-2 mNG NT assay is a biofunctional assay that measures neutralizing antibodies against SARS-CoV-2. This assay is described in Test Method VR-TM-10298. Briefly, [redacted]

[redacted]

This validation study evaluated assay [redacted] linearity, precision, limit of detection, and intermediate precision. The [redacted] linearity and precision results were used to define the limits of quantitation and extravariability criterion.

4.2 Experimental Design

Validation of the SARS-CoV-2 mNG NT assay was performed as described in the validation protocol (VR-MVP-10074).

[redacted]

[redacted]

5.1 Introduction

Test Method TM100010380 "Determination [redacted] PF-07302048

[redacted]

[redacted]

[redacted]

[redacted]

5.2 Validation Outline

This validation report contains the results of validation study conducted according to the following method validation protocols:

- VAL100138078, V1.0 Protocol for co-validation of test method TM100010380, which was the original method validation protocol to evaluate repeatability, reproducibility, specificity, and detection limit,
- INX100459445, V1.0 Amendment for protocol for co-validation of test method TM100010380, which was an amendment to original method validation protocol VAL100138078 to evaluate the robustness of [redacted] during reproducibility studies.

In routine tests, the assay is analyzed [redacted]

[redacted]

[redacted]

6. CONCLUSIONS

This review memo focuses on the validation of the SARS-CoV-2 mNG NT assay for the detection of serum antibodies capable of neutralizing SARS-CoV-2 and the validation of the [redacted] potency assay, TM100010380 v5.0, for determination of the [redacted] of PF-07302048 by [redacted].

With respect to the validation of the SARS-CoV-2 mNG NT assay, results from the validation study suggest acceptable accuracy and precision. The LOD, LLOQ, and ULOQ were determined to be [redacted], respectively. The LOD study demonstrated [redacted]

With respect to the validation of the [redacted] assay, results from the validation study suggest acceptable specificity and is robust to [redacted]. The detection limit (DL) was determined to be [redacted]. The repeatability and reproducibility of the assay were estimated to be [redacted], respectively. Since the [redacted] assay was validated as a limit test, the repeatability and reproducibility results were evaluated for information only.

In conclusion, I consider both the SARS-CoV-2 mNG NT and [redacted] assays adequate for their intended uses in support of this BLA.

Application Type	BLA, Original Application
STN	125742/0
CBER Received Date	May 18, 2021
PDUFA Goal Date	January 16, 2022
Division / Office	DVRPA/OVRR
Committee Chair	Ramachandra Naik
Clinical Reviewer(s)	Ann Schwartz; Susan Wollersheim
Project Manager	Michael Smith; Laura Gottschalk
Priority Review	Yes
Reviewer Name	Ye Yang, Mathematical Statistician, DB/VEB
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Concurring Reviewer, DB/VEB
Supervisory Concurrence	Tsai-Lien Lin, Branch Chief, DB/VEB
Supervisory Concurrence	John Scott, Director, DB
Applicant	BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)
Established Name	COVID-19 Vaccine, mRNA
(Proposed) Trade Name	COMIRNATY
Dosage Form(s) and Route(s) of Administration	Injectable Suspension, Intramuscular
Dosing Regimen	Two 0.3 mL doses, three weeks apart
Indication(s) and Intended Population(s)	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older

Table of Contents

Glossary **3**

1. Executive Summary **4**

2. Clinical and Regulatory Background **4**

3. Submission Quality and Good Clinical Practices **5**

3.1 Submission Quality and Completeness 5
3.2 Compliance With Good Clinical Practices And Data Integrity 5

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines **5**

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

5.1 Review Strategy 5
5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review 5
5.3 Table of Studies/Clinical Trials 6

6. Discussion of Individual Studies/Clinical Trials **6**

6.1 Study C4591001 6
6.1.1 Objectives 6
6.1.2 Design Overview 6
6.1.3 Population 7
6.1.4 Study Treatments or Agents Mandated by the Protocol 7
6.1.6 Sites and Centers 7
6.1.7 Surveillance/Monitoring 7
6.1.8 Endpoints and Criteria for Study Success 7
6.1.9 Statistical Considerations & Statistical Analysis Plan 8
6.1.10 Study Population and Disposition 8
6.1.11 Efficacy Analyses 9
6.1.12 Safety Analyses 9

7. Integrated Overview of Efficacy **15**

8. Integrated Overview of Safety **15**

9. Additional Statistical Issues **15**

10. Conclusions **15**

10.1 Statistical Issues and Collective Evidence 15
10.2 Conclusions and Recommendations 16

GLOSSARY

ADaM	Analysis Data Model
AE	Adverse Event
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
COVID-19	Coronavirus Disease 2019
EUA	Emergency Use Authorization
HIV	Human Immunodeficiency Virus
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SDTM	Study Data Tabulation model

1. Executive Summary

Pfizer submitted a Biologics License Application (BLA 125742.0) on May 18, 2021 to seek licensure of the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) for active immunization to prevent Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The BLA is supported by safety, efficacy, and immunogenicity data from two ongoing studies (C4591001 and BNT-162-01). This statistical review focuses on safety data from subjects aged 16 years and above in the Phase 2/3 part of Study C4591001 collected up to the March 13, 2021 data cut-off.

Study C4591001 is an ongoing, randomized, placebo-controlled, observer-blinded Phase 1/2/3 study being conducted in the United States, Argentina, Brazil, Germany, South Africa, and Turkey. In the Phase 2/3 portion of the study, 44,165 subjects aged 16 and above were randomized 1:1 to receive two doses of BNT162b2 or placebo 21 days apart. Randomization was stratified by age group (younger adults 18 through 55 years of age and older adults >55 years of age; adolescents 16 to 17 were later added via a protocol amendment) with 40.6% of the final study population being older adults. Since December 14, 2020, following issuance of the EUA, participants 16 years of age and older were systematically unblinded when eligible per local recommendations and offered BNT162b2 vaccination if they had been randomized to placebo.

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

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

2. Clinical and Regulatory Background

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

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

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to Haecin Chun's Bioresearch Monitoring inspections review memo.

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

Please refer to reviews of other review disciplines.

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

5.1 Review Strategy

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

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

The following documents submitted to the BLA are reviewed:

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

Module 2. Common Technical Document Summaries

- Clinical Overview
- Summary of Clinical Safety

Module 5. Clinical Study Reports

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

Module 1. Administrative Information and Prescribing Information

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

Module 1. Administrative Information and Prescribing Information

- Response to May 18, 2021 Information Request

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

Module 1. Administrative Information and Prescribing Information

- Response to July 29, 2021 Information Request

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

Module 5. Clinical Study Reports

- C4591001 – 508 Safety Tables

5.3 Table of Studies/Clinical Trials

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

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

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

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

6. Discussion of Individual Studies/Clinical Trials

6.1 Study C4591001

Title of Study: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

First Subject First Visit: April 29, 2020

Data Cut-off: Mach 13, 2021

6.1.1 Objectives

Primary Safety Objective (Phase 2/3):

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

6.1.2 Design Overview

Study C4591001 is an ongoing, randomized, placebo-controlled, observer-blinded Phase 1/2/3 study being conducted in the United States, Argentina, Brazil, Germany, South Africa, and Turkey. In the Phase 2/3 portion of the study, 43,998 subjects were planned

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

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

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

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

6.1.3 Population

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

6.1.4 Study Treatments or Agents Mandated by the Protocol

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

6.1.6 Sites and Centers

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

6.1.7 Surveillance/Monitoring

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

6.1.8 Endpoints and Criteria for Study Success

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

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

6.1.9 Statistical Considerations & Statistical Analysis Plan

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

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

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

Table 2. Subject Disposition

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

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

6.1.10.1.1 Demographics

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

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

Table 3. Demographics Characteristics of the Safety Population

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

Source: Table 4 of Summary of Clinical Safety.

6.1.11 Efficacy Analyses

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

6.1.12 Safety Analyses

Solicited Local and Systemic Reactions

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

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

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

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

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

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

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

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

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

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

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

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

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

Reviewer Comment:

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

Unsolicited Safety

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

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

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

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

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

Reviewer Comments:

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

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

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

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

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

Myocarditis and Pericarditis

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

7. Integrated Overview of Efficacy

No integrated analysis of efficacy was performed.

8. Integrated Overview of Safety

No integrated analysis of safety was performed.

9. Additional Statistical Issues

There are no additional statistical issues.

10. Conclusions

10.1 Statistical Issues and Collective Evidence

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

10.2 Conclusions and Recommendations

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

From: Tierney, Julia
To: Marks, Peter
Cc: Walinsky, Sarah
Subject: RE: Catching up
Date: Monday, July 19, 2021 9:09:00 PM

Happy to chat. I spoke with Janet tonight and she is aware.

From: Marks, Peter [redacted]
Sent: Monday, July 19, 2021 6:18 PM
To: Tierney, Julia [redacted]
Cc: Walinsky, Sarah [redacted]
Subject: FW: Catching up
Dear Julie and Sarah
Thoughts welcome. May be easiest to touch bases by phone. Thanks.
Best Regards,
Peter

From: Marks, Peter
Sent: Monday, July 19, 2021 6:16 PM
To: Gruber, Marion [redacted]>
Subject: RE: Catching up
Dear Marion,
Thanks for all of these questions, all of which are entirely reasonable. I have been giving them some thought and have some thoughts to share with you, for which I would welcome your feedback. Look forward to speaking in the morning.
Best Regards,
Peter

From: Gruber, Marion [redacted]
Sent: Monday, July 19, 2021 6:14 PM
To: Marks, Peter [redacted]
Subject: RE: Catching up
Dear Peter,
I informed DVRPA and DVP management that for the time that I will be [redacted], JW assigned you direct oversight of the Pfizer Corminaty BLA and that Phil will be overseeing other regulatory files. DVRPA and DVP management requested, before they inform their staff, to get clarification on the process that will be followed, specifically:

- How will you be interacting with the review team, i.e., will you be present at all their meetings, will you be directly interacting with the Chair?
- JW mentioned she wants to be briefed on the review process, what would this look like?
- I typically get updates from DVP and DVRPA and also interact with OBE: How do you foresee such interaction?
- Will you be directly interacting with Theresa Finn and Karen Farizo regarding labeling, PerC and getting agreement on potential PMRs?
- Have OBE and OCBQ be informed?

As you can imagine, there is a great deal of Angst and uncertainty and I would appreciate if we can discuss the above in our meeting tomorrow. I need to provide reassurance to the team. Also, it is not clear to me whether I, and for that matter Phil, will be put back in charge

regarding this BLA once I return [redacted].
Thank you,
Marion

From: Marks, Peter [redacted]
Sent: Monday, July 19, 2021 11:32 AM
To: Gruber, Marion [redacted]
Subject: Catching up

Dear Marion,

Just wanted to follow up on this morning's meeting with Janet. I appreciate all of the work that you and OVRR have done here and want to try to connect tomorrow to make sure that a number of different issues that are pending. I am open from 7 to 7:30 or 8 to 9. Just let me know what might work for you. Also, thanks very much for attending the [redacted] meeting this afternoon. Though I may spend more than the hour with them, I will let them know that some team members will need to leave after and hour. Thanks again for doing this.

Best Regards,
Peter

From: Sheehy, Janice
To: Tierney, Julia
Subject: RE: Meeting w CBER
Date: Friday, July 16, 2021 3:06:55 PM

Yes, will do, thanks. -j

From: Tierney, Julia [redacted]
Sent: Friday, July 16, 2021 3:06 PM
To: Sheehy, Janice <Janice.Sheehy@fda.hhs.gov>
Subject: RE: Meeting w CBER
Thanks. And assume meeting will not be forwardable. Thanks.

From: Sheehy, Janice [redacted]
Sent: Friday, July 16, 2021 3:05 PM
To: Tierney, Julia [redacted]
Subject: FW: Meeting w CBER
FYI

From: Marks, Peter [redacted]
Sent: Friday, July 16, 2021 3:04 PM
To: Sheehy, Janice [redacted] Jenkins, Charlene [redacted]; Grantham, Gloria [redacted]
Cc: Walinsky, Sarah [redacted]; Copeland, Jakea [redacted]
Subject: RE: Meeting w CBER
Dear Janice,
Please just invite Marion Gruber and me.
Best Regards,
Peter

From: Sheehy, Janice [redacted]
Sent: Friday, July 16, 2021 3:02 PM
To: Jenkins, Charlene [redacted] Grantham, Gloria [redacted]
Cc: Marks, Peter [redacted] Walinsky, Sarah [redacted] Copeland, Jakea < [redacted]
Subject: RE: Meeting w CBER
Hi, just checking back in please for the names of the CBER folks to be included in Monday's 8:30am.
Thanks so much! -janice

From: Jenkins, Charlene [redacted]
Sent: Tuesday, July 13, 2021 7:45 AM
To: Sheehy, Janice [redacted]
Cc: Marks, Peter [redacted] Walinsky, Sarah [redacted]
Subject: RE: Meeting w CBER
Good Morning Janice,
The best time for Dr. Marks would be:
Monday, July 19: 8:30-9:00am
Sincerely,
Charlene

From: Sheehy, Janice [redacted]
Sent: Tuesday, July 13, 2021 7:13 AM
To: Jenkins, Charlene [redacted]
Cc: Marks, Peter [redacted] Walinsky, Sarah [redacted]
Subject: FW: Meeting w CBER

Good morning, Charlene!
Per Julie's email below, would you please let me know which date/time (30-minute block) works best for Dr. Marks:
Friday, July 16: 2:00-3:00pm, 4:00-5:00pm
Monday, July 19: 8:30-9:00am, 9:30-10:00am
I will wait to hear who Dr. Marks would like to have included on the calendar invite.
Thank you!
-janice

From: Tierney, Julia [redacted]
Sent: Monday, July 12, 2021 9:06 PM
To: Copeland, Jakea [redacted]; Sheehy, Janice [redacted]>
Subject: Meeting w CBER

Can you please find 30 minutes on Friday 7/16 afternoon or Monday 7/19 morning for JW to meet w Peter Marks and others in CBER to discuss vaccine review? For now, let's just hold on JW, mine, and Peter's calendars and then Peter can tell us who he'd like to invite from his staff.

From: Marks, Peter
To: Woodcock, Janet; Tierney, Julia
Subject: RE: Pfizer COVID-19 vaccine BLA review timeline
Date: Friday, July 16, 2021 11:20:48 AM
Attachments: image001.png

Dear Janet,
Thanks. In my mind, the issue is that for four weeks, aside from mandatory IND review and safety work and continuing work on one PDUFA goal vaccine, all available hands in the office of vaccines, epi and my immediate office should be working to get the Pfizer vaccine done. I am putting together a notional Gantt chart that I will refine.
I am committed to getting this done timely – we will make it happen.
(I have Warp Speed to live up to!)
Best Regards,
Peter

From: Woodcock, Janet [redacted]
Sent: Friday, July 16, 2021 11:10 AM
To: Tierney, Julia [redacted]
Cc: Marks, Peter [redacted]
Subject: RE: Pfizer COVID-19 vaccine BLA review timeline
Well they seem open to additional support on other vaccine efforts, and are already working with CDER office of computational science, which is a good thing. Peter you can find out more when you take over. jw

---

From: Tierney, Julia [redacted]
Sent: Friday, July 16, 2021 9:26 AM
To: Woodcock, Janet [redacted]
Cc: Marks, Peter [redacted]
Subject: FW: Pfizer COVID-19 vaccine BLA review timeline
Just reupping

From: Marks, Peter [redacted]
Sent: Thursday, July 15, 2021 10:11 AM
To: Woodcock, Janet [redacted]
Cc: Tierney, Julia <[redacted]
Subject: FW: Pfizer COVID-19 vaccine BLA review timeline
Dear Janet,
Perhaps we can have a brief call tomorrow? I can fill you in on the conversation that I had with Marion and Phil subsequent to their sending me this document. I have asked them to provide me with a timeline of milestones, and they are meeting with the review team today to be able to do so tomorrow morning. That said, they are intransigent at this time on the Sept 15 date.
Thanks very much.
Best Regards,
Peter

From: Gruber, Marion [redacted]
Sent: Thursday, July 15, 2021 8:00 AM
To: Marks, Peter [redacted] Witten, Celia (CBER) [redacted]

Cc: Krause, Philip [redacted]

Subject: Pfizer COVID-19 vaccine BLA review timeline

Dear Peter,

Phil and I have further discussed with DVRPA and DVP management the review timeline for the above BLA. As you know we are targeting September 15 as the ADD. It will not be possible to move the ADD up further without cutting corners and lowering our review standards and that I would not be able to defend. We have described our rationale and logic in the attached memo. Feel free to share with JW.

Marion

Marion F. Gruber, Ph.D

Director

Office of Vaccines Research & Review

Center for Biologics Evaluation & Research

Food & Drug Administration, DHHS

10903 New Hampshire Ave.

Building 71, Rm. 3230

Silver Spring, Maryland 20993

Tel.: [redacted]

Email: [redacted]

From: Woodcock, Janet
To: Marks, Peter; Tierney, Julia
Subject: RE: Pfizer COVID-19 vaccine BLA review timeline
Date: Thursday, July 15, 2021 10:12:49 AM
Attachments: image001.png

Sure we can set up some time. jw

From: Marks, Peter [redacted]
Sent: Thursday, July 15, 2021 10:11 AM
To: Woodcock, Janet [redacted]
Cc: Tierney, Julia [redacted]
Subject: FW: Pfizer COVID-19 vaccine BLA review timeline

Dear Janet,

Perhaps we can have a brief call tomorrow? I can fill you in on the conversation that I had with Marion and Phil subsequent to their sending me this document. I have asked them to provide me with a timeline of milestones, and they are meeting with the review team today to be able to do so tomorrow morning. That said, they are intransigent at this time on the Sept 15 date.

Thanks very much.

Best Regards,

Peter

From: Gruber, Marion [redacted]
Sent: Thursday, July 15, 2021 8:00 AM
To: Marks, Peter [redacted]; Witten, Celia (CBER) [redacted]
Cc: Krause, Philip [redacted]>
Subject: Pfizer COVID-19 vaccine BLA review timeline

Dear Peter,

Phil and I have further discussed with DVRPA and DVP management the review timeline for the above BLA. As you know we are targeting September 15 as the ADD. It will not be possible to move the ADD up further without cutting corners and lowering our review standards and that I would not be able to defend. We have described our rationale and logic in the attached memo. Feel free to share with JW.

Marion

Marion F. Gruber, Ph.D.
Director
Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993
Tel.: [redacted]
Email: [redacted]

From: Woodcock, Janet
To: Tierney, Julia
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines
Date: Saturday, July 17, 2021 1:07:11 PM
Attachments: image001.png

Great, thanks. jw

From: Tierney, Julia [redacted]
Sent: Saturday, July 17, 2021 12:45 PM
To: Woodcock, Janet [redacted] Marks, Peter [redacted]>
Subject: Re: Pfizer COVID-19 vaccine BLA review timelines
Sent an invite for 2

From: Woodcock, Janet [redacted]
Sent: Saturday, July 17, 2021 12:01:37 PM
To: Marks, Peter <[redacted] Tierney, Julia <[redacted]
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines
Agree. Anytime before 5 is good. wj

From: Marks, Peter [redacted]
Sent: Saturday, July 17, 2021 11:56 AM
To: Woodcock, Janet [redacted]; Tierney, Julia <[redacted]>
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines
Dear Janet,
Totally fine with whatever you want to do with this. Based on what Marion provided, I think that shaving three weeks off is truly possible. We just need to motivate the team around this cause – that is something I actually know how to do as a leader (a la the beginning of Warp Speed and my previous work in industry).
I could do this afternoon anytime after 2 PM. Also could probably make 1 pm tomorrow work.
Best Regards,
Peter

From: Woodcock, Janet <[redacted]
Sent: Saturday, July 17, 2021 11:52 AM
To: Tierney, Julia <[redacted] Marks, Peter [redacted]
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines
This afternoon or tomorrow is good for me. Marion has asked to include Phil Krause in the meeting with me. jw

From: Tierney, Julia [redacted]
Sent: Friday, July 16, 2021 6:56 PM
To: Marks, Peter [redacted] Woodcock, Janet [redacted]
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines
Happy to put a call-in on over the weekend for us whenever works best for the two of you.

From: Marks, Peter [redacted]
Sent: Friday, July 16, 2021 6:08 PM
To: Woodcock, Janet <[redacted] Tierney, Julia <[redacted]
Subject: FW: Pfizer COVID-19 vaccine BLA review timelines

Dear Janet and Julie,
Please see the attached. Marion finally provided this timeline. I can already see a number of potential efficiencies. Perhaps we can discuss over the weekend briefly in preparation for Monday?
Thanks.
Best Regards,
Peter

From: Gruber, Marion <[redacted]
Sent: Friday, July 16, 2021 5:39 PM
To: Marks, Peter [redacted]>
Cc: Malarkey, Mary [redacted]; Anderson, Steven [redacted] Krause, Philip [redacted]>
Subject: Pfizer COVID-19 vaccine BLA review timelines

Dear Peter,
As requested, see attached our projected timelines for completing currently ongoing reviews, tasks and responsibilities for the above BLA. Of note, the bar graphs reflect targeted completion dates, some of these pending timely sponsor response to information request which we have been and are sending as we review the info contained in the submission. The target ADD is September 15. Note that DBSQC DS and DP testing will not be completed at that time because of reagent shortage.
Marion
[I saw earlier today that CNN announced that this review will be completed within 2 months; thus, Sep 15, even though ambitious, is within this projected timeline.]

Marion F. Gruber, Ph.D
Director
Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993
Tel.: [redacted]

From: Woodcock, Janet
To: Marks, Peter; Tierney, Julia
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines
Date: Saturday, July 17, 2021 12:01:39 PM
Attachments: image001.png

Agree. Anytime before 5 is good. wj

From: Marks, Peter [redacted]
Sent: Saturday, July 17, 2021 11:56 AM
To: Woodcock, Janet [redacted]; Tierney, Julia [redacted]>
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines

Dear Janet,

Totally fine with whatever you want to do with this. Based on what Marion provided, I think that shaving three weeks off is truly possible. We just need to motivate the team around this cause – that is something I actually know how to do as a leader (a la the beginning of Warp Speed and my previous work in industry).

I could do this afternoon anytime after 2 PM. Also could probably make 1 pm tomorrow work.

Best Regards,

Peter

From: Woodcock, Janet [redacted]>
Sent: Saturday, July 17, 2021 11:52 AM
To: Tierney, Julia [redacted]; Marks, Peter <[redacted]>
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines

This afternoon or tomorrow is good for me. Marion has asked to include Phil Krause in the meeting with me. jw

From: Tierney, Julia <[redacted]>
Sent: Friday, July 16, 2021 6:56 PM
To: Marks, Peter [redacted]; Woodcock, Janet [redacted]
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines

Happy to put a call-in on over the weekend for us whenever works best for the two of you.

From: Marks, Peter <[redacted]
Sent: Friday, July 16, 2021 6:08 PM
To: Woodcock, Janet <[redacted] Tierney, Julia <[redacted]
Subject: FW: Pfizer COVID-19 vaccine BLA review timelines

Dear Janet and Julie,

Please see the attached. Marion finally provided this timeline. I can already see a number of potential efficiencies. Perhaps we can discuss over the weekend briefly in preparation for Monday?

Thanks.

Best Regards,

Peter

From: Gruber, Marion [redacted]
Sent: Friday, July 16, 2021 5:39 PM
To: Marks, Peter [redacted]
Cc: Malarkey, Mary <[redacted] Anderson, Steven [redacted] Krause, Philip [redacted]

Subject: Pfizer COVID-19 vaccine BLA review timelines

Dear Peter,

As requested, see attached our projected timelines for completing currently ongoing reviews, tasks and responsibilities for the above BLA. Of note, the bar graphs reflect targeted completion dates, some of these pending timely sponsor response to information request which we have been and are sending as we review the info contained in the submission. The target ADD is September 15. Note that DBSQC DS and DP testing will not be completed at that time because of reagent shortage.

Marion

[I saw earlier today that CNN announced that this review will be completed within 2 months; thus, Sep 15, even though ambitious, is within this projected timeline.]

Marion F. Gruber, Ph.D
Director
Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993
Tel.: [redacted]
Email: [redacted]

From: Woodcock, Janet
To: Marks, Peter; Tierney, Julia
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines
Date: Saturday, July 17, 2021 11:53:05 AM
Attachments: image001.png

Tomorrow 1 or 2 PM? jw

From: Marks, Peter [redacted]
Sent: Friday, July 16, 2021 7:19 PM
To: Tierney, Julia [redacted]; Woodcock, Janet [redacted]
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines

Dear Julie,

Pretty much any time that can work for Janet could work for me this weekend.

Best Regards,

Peter

From: Tierney, Julia [redacted]
Sent: Friday, July 16, 2021 6:56 PM
To: Marks, Peter [redacted]; Woodcock, Janet <[redacted]
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines

Happy to put a call-in on over the weekend for us whenever works best for the two of you.

From: Marks, Peter [redacted]>
Sent: Friday, July 16, 2021 6:08 PM
To: Woodcock, Janet [redacted]; Tierney, Julia <[redacted]>
Subject: FW: Pfizer COVID-19 vaccine BLA review timelines

Dear Janet and Julie,

Please see the attached. Marion finally provided this timeline. I can already see a number of potential efficiencies. Perhaps we can discuss over the weekend briefly in preparation for Monday?

Thanks.

Best Regards,

Peter

From: Gruber, Marion <[redacted]
Sent: Friday, July 16, 2021 5:39 PM
To: Marks, Peter [redacted]
Cc: Malarkey, Mary [redacted]; Anderson, Steven [redacted] Krause, Philip <[redacted]>
Subject: Pfizer COVID-19 vaccine BLA review timelines

Dear Peter,

As requested, see attached our projected timelines for completing currently ongoing reviews, tasks and responsibilities for the above BLA. Of note, the bar graphs reflect targeted completion dates, some of these pending timely sponsor response to information request which we have been and are sending as we review the info contained in the submission. The target ADD is September 15. Note that DBSQC DS and DP testing will not be completed at that time because of reagent shortage.

Marion

[I saw earlier today that CNN announced that this review will be completed within 2 months; thus, Sep 15, even though ambitious, is within this projected timeline.]

Marion F. Gruber, Ph.D
Director
Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993
Tel.: [redacted]
Email: [redacted]

From: Woodcock, Janet
To: Tierney, Julia; Marks, Peter
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines
Date: Saturday, July 17, 2021 11:52:01 AM
Attachments: image001.png

This afternoon or tomorrow is good for me. Marion has asked to include Phil Krause in the meeting with me. jw

From: Tierney, Julia <[redacted]>
Sent: Friday, July 16, 2021 6:56 PM
To: Marks, Peter [redacted]; Woodcock, Janet [redacted]>
Subject: RE: Pfizer COVID-19 vaccine BLA review timelines
Happy to put a call-in on over the weekend for us whenever works best for the two of you.

From: Marks, Peter <[redacted]>
Sent: Friday, July 16, 2021 6:08 PM
To: Woodcock, Janet [redacted]; Tierney, Julia <[redacted]
Subject: FW: Pfizer COVID-19 vaccine BLA review timelines
Dear Janet and Julie,
Please see the attached. Marion finally provided this timeline. I can already see a number of potential efficiencies. Perhaps we can discuss over the weekend briefly in preparation for Monday?
Thanks.
Best Regards,
Peter

From: Gruber, Marion [redacted]
Sent: Friday, July 16, 2021 5:39 PM
To: Marks, Peter [redacted]>
Cc: Malarkey, Mary [redacted]; Anderson, Steven [redacted]>; Krause, Philip [redacted]
Subject: Pfizer COVID-19 vaccine BLA review timelines
Dear Peter,
As requested, see attached our projected timelines for completing currently ongoing reviews, tasks and responsibilities for the above BLA. Of note, the bar graphs reflect targeted completion dates, some of these pending timely sponsor response to information request which we have been and are sending as we review the info contained in the submission. The target ADD is September 15. Note that DBSQC DS and DP testing will not be completed at that time because of reagent shortage.
Marion
[I saw earlier today that CNN announced that this review will be completed within 2 months; thus, Sep 15, even though ambitious, is within this projected timeline.]

Marion F. Gruber, Ph.D
Director
Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993

Tel.: [redacted]
[redacted]

From: Marks, Peter
To: Woodcock, Janet
Cc: Tierney, Julia
Subject: FW: Pfizer COVID-19 vaccine BLA review timeline
Date: Thursday, July 15, 2021 10:11:27 AM
Attachments: image001.png
Pfizer COVID-19 vaccine BLA review timeline.docx

Dear Janet,

Perhaps we can have a brief call tomorrow? I can fill you in on the conversation that I had with Marion and Phil subsequent to their sending me this document. I have asked them to provide me with a timeline of milestones, and they are meeting with the review team today to be able to do so tomorrow morning. That said, they are intransigent at this time on the Sept 15 date.

Thanks very much.

Best Regards,

Peter

From: Gruber, Marion [redacted]>
Sent: Thursday, July 15, 2021 8:00 AM
To: Marks, Peter <[redacted]; Witten, Celia (CBER) [redacted]
Cc: Krause, Philip <[redacted]
Subject: Pfizer COVID-19 vaccine BLA review timeline

Dear Peter,

Phil and I have further discussed with DVRPA and DVP management the review timeline for the above BLA. As you know we are targeting September 15 as the ADD. It will not be possible to move the ADD up further without cutting corners and lowering our review standards and that I would not be able to defend. We have described our rationale and logic in the attached memo. Feel free to share with JW.

Marion

Marion F. Gruber, Ph.D
Director
Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993
Tel.: [redacted]

Pfizer COVID-19 STN 125742.0 BLA target AD: 09/15/2021

OVRR's decision to expedite the planned completion of the Pfizer BLA review to September 15, 2021, was based on a careful consideration of the steps that need to take place. OVRR's logic is outlined below.

The Pfizer BLA is a complex BLA

Of note, the pivotal study supporting the BLA was conducted in over 40,000 subjects. To provide additional assurance of the safety and effectiveness of this product that is currently administered to millions of subjects in the US and globally, we requested 6 months safety follow-up to support the BLA as opposed to the 2 months safety follow-up that supported the EUA. The applicant has also submitted additional efficacy data on substantial numbers of cases in vaccine and control groups that were not available with the EUA request submission and data on post-authorization safety experience. These additional data are substantial and enable additional important analyses.

The BLA merits a complete and thorough review

OVRR's reviews of vaccine BLAs, unlike those of regulators in other countries, do not rely on summary tables that are generated by the developer. OVRR views it as essential that review of the safety and efficacy data not only includes an evaluation of the data analyses conducted by the applicant, but also includes CBER's own analysis of the datasets submitted by Pfizer. This has been OVRR's standard for all other BLAs, and while time-consuming, OVRR believes that confidence in COVID vaccines would not be served by starting to cut corners on this review.

While the efficacy data may appear simple to evaluate, longer term follow-up of placebo-controlled data provides essential information that may be of high relevance to discussions about boosting. Moreover, the safety data represent the only placebo-controlled data we have on the safety of this vaccine. These placebo-controlled data are likely to be free of biases that might occur in post-licensure observational studies, so it is imperative to carefully review the reported adverse events, including evaluation of the sponsor's attribution of these events (or lack thereof) to vaccination.

As compared with other BLAs, the proposed completion date of Sept 15 would be unprecedented

The Pfizer COVID-19 BLA received priority designation, allowing 8 months for CBER review and is a "rolling" BLA. Note that the final piece of the roll was received on May 18, 2021 at which point the review clock started. We are targeting September 15, 2021 as the date we will be taking regulatory action, which is less than 4 months from the date the last section of the BLA was submitted. Thus, we will be reviewing this very large and complex BLA in a 1/3 rd of the time typically allowed for a BLA standard application and in less than half the time allocated for a priority review application.

This is possible only with deprioritization of other reviews, including some related to COVID, and reassignment of work to other experienced medical officers.

At this time, while we have hired additional medical officers, we have a limited number of clinical reviewers with the specialized experience needed to assess complex preventive vaccine files requiring comprehensive review, such as those for COVID vaccines that have progressed to pursuing an EUA or BLA. Addressing the high volume of COVID-related work has necessitated deprioritizing some vaccine files.

In addition, we have de-prioritized certain COVID-vaccine related submissions (including some from Pfizer), e.g., amendments pertaining to protocols and studies in pregnant women and immunocompromised subjects, until such time that the BLA review is completed.

However, Pfizer requested advice on 4 booster protocols and advice on the safety data base to support use of the COVID-19 vaccine in pediatric populations 6 months – 12 years of age. These cannot be deprioritized and will need to be reviewed by staff and overseen by supervisors familiar with the Pfizer COVID vaccine IND ad EUA, concurrent with review activities for the Pfizer COVID-19 BLA.

While it was not possible to completely reassign other COVID-19 vaccine- related and non-COVID vaccine-related review work for the MOs assigned to the Pfizer BLA, workload adjustments have been made to allow them to focus nearly exclusively on review of this BLA.

In addition, if the trajectory of the pandemic/emergence of variant of concerns (i.e., delta variant) necessitates the review of EUA amendments for booster doses for the currently U.S. EUA authorized COVID-19 vaccines, from a public health perspective, these reviews will need to take priority over completing the BLA review by September 15, 2021.

Additional support from outside OVRR will not speed up the review

Review efforts for the Pfizer COVID-19 vaccine BLA in the various disciplines, including CMC, nonclinical, PV and facility is ongoing. Information requests have been sent to Pfizer as part of these reviews, and responses are pending. However, the rate-limiting step in regard to potentially accelerating the review timeline to earlier than September 15 is the clinical review, considering the complexity of the clinical safety and effectiveness data. The safety review encompasses a critical evaluation and interpretation of solicited and unsolicited safety data and SAES, and clinical AEs of interest including, but not limited to, the myocarditis signal that has been observed following the administration of the Pfizer COVID-19 vaccine under EUA. We are also performing subgroup analyses of safety and effectiveness data for race, ethnicity and subjects with underlying conditions. Completion of these reviews may require additional correspondence with the sponsor. We hope that reviewers will be able to complete their detailed review memos for the various review activities by the beginning of September as planned. After this has been finished, there are important additional review activities to be completed, including label

negotiations, supervisory review, SBRA preparation, etc. such that it would not be possible to issue the license until September 15.

The experienced MOs assigned to this file are working closely with the data analytics team in CDER-OCS and staff in CBER/OBE who are supporting their review efforts. The need for coordination of evaluation and consistency within the review would lead to diminishing returns if additional staff would be added to this effort. In addition, the reviews have already been initiated and sections of the review are being written as they are completed. Other sections depend on the reviews of the earlier sections, so those parts of the review cannot be completed until the earlier parts of the review have been done, and because they need to take the subtleties of the earlier parts into account, cannot as reliably be performed by medical officers who are new to the file. Thus, assigning additional MOs (even if experienced) to assist in review of the Pfizer COVID vaccine BLA, it is likely that the review effort would be will delayed rather than expedited the review effort as these reassigned individuals would need to familiarize themselves with the file.

Furthermore, reassignment of experienced medical officers to the Pfizer BLA would lead to a cascade of further reassignments and their own assignments will be delayed ultimately leading to an increase in back-log including critical ongoing review activities to support:

- Many anticipated several BLA submissions in in 3/4Q of 2021 including the BLAs for the [redacted] and BLAs for [redacted] all of which are likely to qualify for priority review designation
- The [redacted] BLA,
- Several BLA supplements including an efficacy supplement for [redacted] for the pediatric population,
- Efficacy supplements for [redacted] and
- Booster protocols for the Pfizer, [redacted] COVID EUAs.

In summary, it is not possible to further abbreviate the BLA review timeline for the Pfizer COVID-19 vaccine BLA, our target review date for this file remains September 15, 2021.

Additional support from outside OVRR, if effectively used, might reduce the need to deprioritize certain submissions.

Going forward, OVRR will continue to assign lower priority INDs (including COVID vaccines submitted by small entities and academic investigators) to less experienced staff. Some may need to be deprioritized in order to allow our most experienced reviewers to focus on the submissions that have the greatest public health importance.

In addition, to be able to cope with its heavy and steadily increasing regulatory workload, the following is suggested:

- Hiring or assigning review staff from other offices/centers to support review activities regarding lower priority non-COVID files (e.g., [redacted] so that staff familiar with the COVID -19 vaccine files can continue to focus their review activities on these submissions,
- For CBER to hire additional program analysts to perform data analytics to support MO review activities
- Extension of the J review contract by one year
- For CBER to provide adequate IT support to its staff. It has been our experience that staff who need their laptops refreshed are receiving sub-standard equipment, i.e., refurbished computers that present with multiple problems. As a consequence of this being an Agency-wide issue, ERIC is backed up and cannot provide timely support. This has caused delays in the completion of review assignments.

From: Marks, Peter
To: Hussey, Deirdre
Cc: Walinsky, Sarah
Subject: FW: Pfizer COVID-19 vaccine BLA review timeline
Date: Friday, July 16, 2021 9:48:15 AM
Attachments: image001.png
Pfizer COVID-19 vaccine BLA review timeline.docx
Review timeline.msg

Dear Deirdre,

I am copying this to you because I think that it is important to document that despite repeated verbal attempts, and as documented in the attached email, I have asked Marion for a timeline that would help justify the September 15 data that she provides for completion of the review.

To further expedite the Pfizer BLA review, during the past month I have also repeatedly offered Marion additional resources from the center and my immediate office, some of whom have deep experience in vaccines. However, she had declined, stating that this would not help.

When asked how many clinical reviewers are working on the file, Marion has told me that there are two, and I have questioned why more could not be placed on the file to assist, but she states that does not feel that this would help.

Yesterday, 7/15, with Celia on the line, I reminded Marion that I asked for a timeline of activities, and she said that she would speak to the review team the evening of 7/15 and get back to me. However, she also noted that she didn't believe that the timelines would change.

In my opinion, the recurrent recent deterioration during the current public health emergency necessitates that we fully mobilize all center resources in order to approve a BLA for a COVID-19 vaccine as rapidly as possible.

I am hoping that Marion will get back to me soon with a timeline that we can discuss.

Best Regards,

Peter

From: Gruber, Marion [redacted]
Sent: Thursday, July 15, 2021 8:00 AM
To: Marks, Peter <[redacted] Witten, Celia (CBER) [redacted]
Cc: Krause, Philip <[redacted]
Subject: Pfizer COVID-19 vaccine BLA review timeline

Dear Peter,

Phil and I have further discussed with DVRPA and DVP management the review timeline for the above BLA. As you know we are targeting September 15 as the ADD. It will not be possible to move the ADD up further without cutting corners and lowering our review standards and that I would not be able to defend. We have described our rationale and logic in the attached memo. Feel free to share with JW.

Marion

Marion F. Gruber, Ph.D
Director
Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993
Tel.: [redacted]

Email: [redacted]

From: Marks, Peter
To: Gruber, Marion
Cc: Walinsky, Sarah
Subject: Review timeline
Date: Thursday, July 8, 2021 12:51:00 PM

Dear Marion,

Thanks so much for the update on the timelines this morning. Regarding the Pfizer review timeline, by early next week would it be possible to get a high level listing of review activities sorted by week over the course of the next two and a half months. I need to be able to demonstrate to Janet that we are diligently pursuing the process, and this would be very helpful. The level of detail would not need to be very great – just key completion milestones such as "completion of clinical review," "completion of labeling negotiation," etc.

Best Regards,

Peter

From: Marks, Peter
To: Tierney, Julia
Subject: FW: Pfizer COVID-19 vaccine BLA review timeline
Date: Thursday, July 15, 2021 8:23:15 AM
Attachments: image001.png
Pfizer COVID-19 vaccine BLA review timeline.docx

Dear Julie,

Let's discuss this morning before I forward this to Janet later. Thanks.

Best Regards,

Peter

From: Gruber, Marion [redacted]
Sent: Thursday, July 15, 2021 8:00 AM
To: Marks, Peter [redacted]; Witten, Celia (CBER) [redacted]
Cc: Krause, Philip [redacted]
Subject: Pfizer COVID-19 vaccine BLA review timeline

Dear Peter,

Phil and I have further discussed with DVRPA and DVP management the review timeline for the above BLA. As you know we are targeting September 15 as the ADD. It will not be possible to move the ADD up further without cutting corners and lowering our review standards and that I would not be able to defend. We have described our rationale and logic in the attached memo. Feel free to share with JW.

Marion

Marion F. Gruber, Ph.D
Director
Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993
Tel.: [redacted]
[redacted]

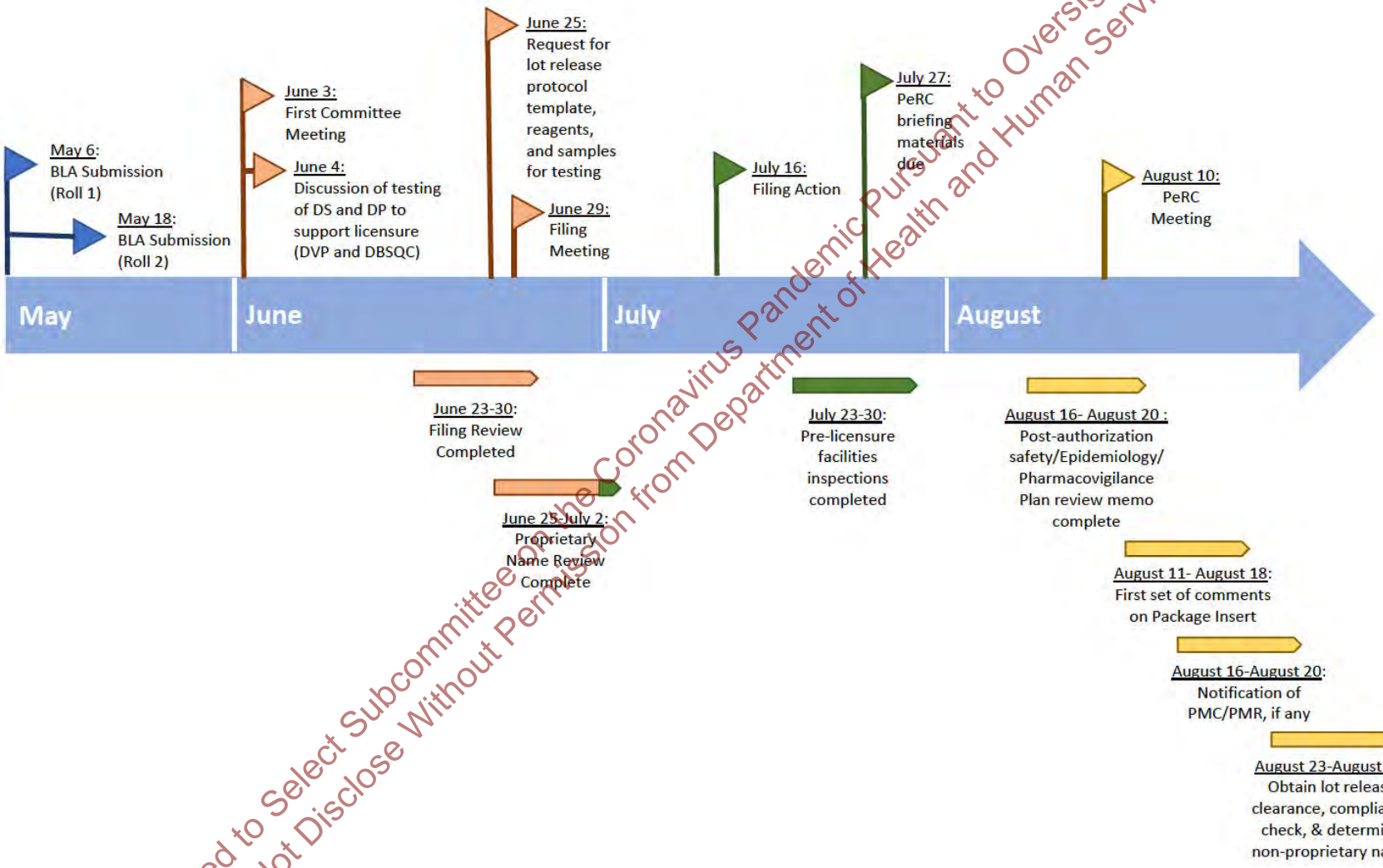
From: Marks, Peter
To: Woodcock, Janet; Tierney, Julia
Subject: FW: Pfizer COVID-19 vaccine BLA review timelines
Date: Friday, July 16, 2021 6:08:12 PM
Attachments: Updated Pfizer COVID Approval Timeline.pptx
image001.png

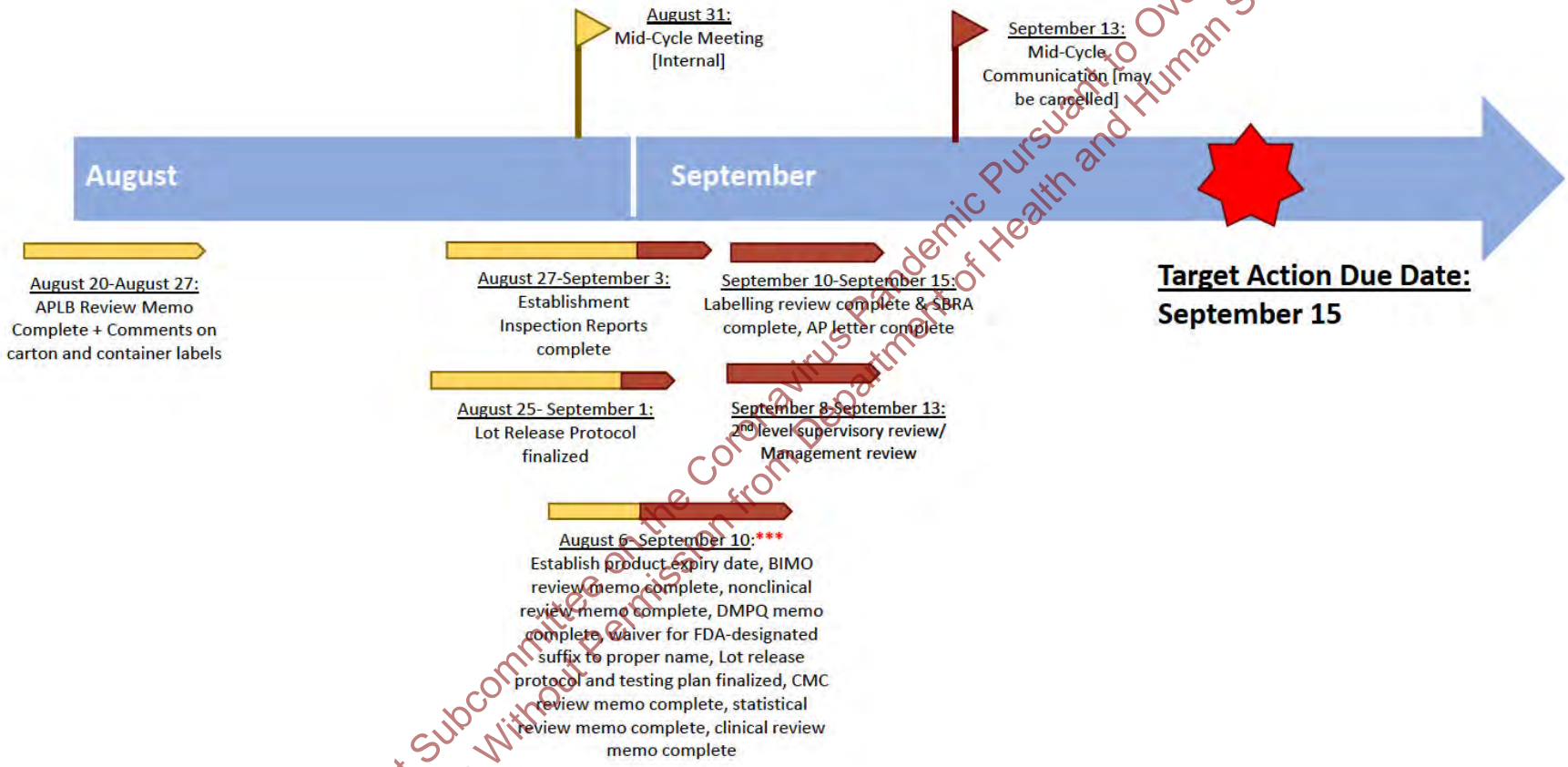
Dear Janet and Julie,
Please see the attached. Marion finally provided this timeline. I can already see a number of potential efficiencies. Perhaps we can discuss over the weekend briefly in preparation for Monday?
Thanks.
Best Regards,
Peter

From: Gruber, Marion [redacted]
Sent: Friday, July 16, 2021 5:39 PM
To: Marks, Peter <P[redacted]
Cc: Malarkey, Mary [redacted]; Anderson, Steven [redacted] Krause, Philip [redacted]
Subject: Pfizer COVID-19 vaccine BLA review timelines

Dear Peter,
As requested, see attached our projected timelines for completing currently ongoing reviews, tasks and responsibilities for the above BLA. Of note, the bar graphs reflect targeted completion dates, some of these pending timely sponsor response to information request which we have been and are sending as we review the info contained in the submission. The target ADD is September 15. Note that DBSQC DS and DP testing will not be completed at that time because of reagent shortage.
Marion
[I saw earlier today that CNN announced that this review will be completed within 2 months; thus, Sep 15, even though ambitious, is within this projected timeline.]

Marion F. Gruber, Ph.D
Director
Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993
Tel.: [redacted]
[redacted]





***Pending timely sponsor response to info requests

From: Sheehy, Janice
To: Tierney, Julia; Woodcock, Janet
Subject: RE: Vaccine Review
Date: Saturday, July 17, 2021 4:37:50 PM

Will do, thanks! -j

From: Tierney, Julia [redacted]
Sent: Saturday, July 17, 2021 2:28 PM
To: Sheehy, Janice [redacted]; Woodcock, Janet [redacted]>
Subject: RE: Vaccine Review
Janice – I spoke with Janet, please extend the invitation to Phil Krause.
Thanks,
Julie

From: Sheehy, Janice [redacted]
Sent: Saturday, July 17, 2021 12:52 PM
To: Woodcock, Janet [redacted]
Cc: Tierney, Julia [redacted]
Subject: RE: Vaccine Review
Thank you, will do.

From: Woodcock, Janet [redacted]
Sent: Saturday, July 17, 2021 11:51 AM
To: Sheehy, Janice [redacted]
Subject: RE: Vaccine Review
Hold off on responding. jw

From: Sheehy, Janice <[redacted]
Sent: Friday, July 16, 2021 6:58 PM
To: Woodcock, Janet [redacted]; Tierney, Julia <[redacted]>
Cc: Copeland, Jakea <[redacted]
Subject: RE: Vaccine Review
Hi, please see Marion's email below. Thanks! -j
-----Original Appointment-----
From: Gruber, Marion [redacted]
Sent: Friday, July 16, 2021 6:45 PM
To: Sheehy, Janice; Olivarria, Frank; Goldie, Christina; Copeland, Jakea
Subject: Accepted: Vaccine Review
When: Monday, July 19, 2021 8:30 AM-9:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: Please see Zoom below
Dear Janet,
Thanks for the invitation. Would it be possible to extent this invitation to my deputy, Dr. Philip Krause ?
Marion

From: Sheehy, Janice
To: Tierney, Julia
Subject: RE: Vaccine Review
Date: Friday, July 16, 2021 7:08:38 PM

Ok thank you.

From: Tierney, Julia [redacted]>
Sent: Friday, July 16, 2021 7:00 PM
To: Sheehy, Janice [redacted]
Subject: RE: Vaccine Review

I'm going to defer to JW on this.

From: Sheehy, Janice [redacted]
Sent: Friday, July 16, 2021 6:58 PM
To: Woodcock, Janet [redacted]; Tierney, Julia [redacted]
Cc: Copeland, Jakea [redacted]
Subject: RE: Vaccine Review

Hi, please see Marion's email below. Thanks! -j

-----Original Appointment-----

From: Gruber, Marion [redacted]
Sent: Friday, July 16, 2021 6:45 PM
To: Sheehy, Janice; Olivarria, Frank; Goldie, Christina; Copeland, Jakea
Subject: Accepted: Vaccine Review
When: Monday, July 19, 2021 8:30 AM-9:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: Please see Zoom below

Dear Janet,
Thanks for the invitation. Would it be possible to extent this invitation to my deputy, Dr. Philip Krause ?
Marion

From: Marks, Peter [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=DFBB2B5BD38445CB9C9ADCA3F72DF53A-MARKSP]
Sent: 7/21/2021 12:10:03 PM
To: Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]; Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]
Subject: RE: Review of Pfizer/BioNTech's BLA for Comirnaty, COVID-19 mRNA vaccine - Summary of meeting dated July 19 2021 - 8:30 am

Dear Julie,

I vote no. Thanks.

Best Regards,
Peter

From: Tierney, Julia [redacted]
Sent: Wednesday, July 21, 2021 12:07 PM
To: Woodcock, Janet [redacted] Marks, Peter <[redacted]
Subject: RE: Review of Pfizer/BioNTech's BLA for Comirnaty, COVID-19 mRNA vaccine - Summary of meeting dated July 19 2021 - 8:30 am

I'm attaching my summary of the meeting for your records. Please let me know if you would like me to circulate to Marion.

From: Gruber, Marion [redacted].gov>
Sent: Wednesday, July 21, 2021 11:59 AM
To: Marks, Peter [redacted]gov>; Woodcock, Janet <[redacted]
Cc: Tierney, Julia <[redacted]; Krause, Philip [redacted]
Subject: Review of Pfizer/BioNTech's BLA for Comirnaty, COVID-19 mRNA vaccine - Summary of meeting dated July 19 2021 - 8:30 am

Dear Janet and Peter,

The following summarizes my understanding of the July 19, 2021, 8:30 am meeting held between you, Phil Krause, Julie Tierney and myself to discuss the review of Pfizer/BioNTech's BLA for Comirnaty, COVID-19 mRNA vaccine. During this meeting, I made reference to the memo that Dr. Krause and I composed and sent to Dr. Marks on July 15, 2021, delineating OVRR's rationale for why the review timeline and target action due date, September 15, 2021, for this BLA cannot be compressed further. To recap, that memo stated that the review requires a thorough evaluation and FDA's own analysis of the safety, effectiveness and manufacturing information submitted to support licensure of this vaccine. This has been OVRR's standard for all other BLAs, and while time-consuming, OVRR believes that public confidence in COVID-19 vaccines would not be served by rushing our review and evaluation of the submitted data. In addition, Dr. Krause and I pointed out the very important regulatory issues that still need to be settled by the time we take action on this BLA—including the pediatric plan — which is becoming increasingly complex in light of increasing evidence of association of this vaccine and development of myocarditis (especially in young males, but also ages included in the BLA indication). This also impacts the finalization of post-marketing requirements and post-marketing commitments. In addition, there are pending information requests to the sponsor, and there will likely be additional information requests based on ongoing review of the data, and the timing of the sponsor response is beyond CBER control.

I reiterated during our meeting that OVRR is targeting September 15, 2021, as the date we will be taking regulatory action, which is less than 4 months from the date the last section of the BLA was submitted. Thus, we will be reviewing this complex BLA with a large amount of data, in a third of the time typically allowed for a BLA standard application and in less than half the time allocated for a priority review application. In response to your questions, I described OVRR's BLA review assignment processes. I emphasized that for this particular BLA, we assigned two experienced medical officers to this file who are working closely with the data analytics team in CDER-OCS and three statisticians from CBER/OBE who are supporting these review efforts. I did not emphasize this during our meeting, but you should also know that our typical review process includes frequent formal and informal communications with managers at all levels and other OVRR experts not directly assigned to the review team. I reiterated that adding staff to this review at this advanced stage would likely slow down the review due to the need to bring new people up to speed. You inquired whether we need additional help and also asked about the expertise of MOs assigned to this file noting that there would be staff in FDA, e.g., pediatric cardiologist that could assist in the review. You expressed concern about the rising COVID-cases in the US and globally, largely caused by the Delta variant and stated your opinion that, absent a license, states cannot require mandatory vaccination and that people hesitant to get an EUA authorized vaccine would be more inclined to get immunized when the product is licensed. You emphasized your interest in licensing this vaccine as soon as possible—a goal that we agree with. We too are concerned about the rising COVID-19 cases in the US, however, our concern is that a review that is hyper-accelerated beyond the already very rapid September 15 target date and as a consequence, may be less thorough than our typical review seems more likely to undermine confidence in the vaccine (and, indeed, in FDA's credibility) than to increase it.

You informed us of your decision that OVRR management and oversight of the BLA review will be delegated to Dr. Marks who will provide you with weekly updates on the review process and ensure that due diligence is exercised while I am away [redacted] You also informed me that Dr. Krause will not be involved in the BLA oversight as he will be overseeing other regulatory and programmatic programs in OVRR. I expressed my disagreement with these decisions because standard procedures are for the deputy Office Director to assume an Acting Role when the Office Director is out of the Office. I note that Dr. Krause is a recognized expert in vaccine regulation, development and very familiar with the scientific and clinical issues presented by this specific vaccine product and that the review team relies on his expertise and guidance.

I would also like to emphasize OVRR staff's dedication and experience in promoting public health by making safe and effective vaccines available for use in the United States. Since I believe we all agree in the importance both of a rapid decision and a thorough scientific and credible review, Dr. Krause and the OVRR staff will stand ready to assist in any way possible to achieve both of these goals. Please confirm that this summary reflects your recollection of this meeting. If it does not, I would appreciate your letting me know any specific areas where your recollection is different.

Thank you,
Marion

Marion F. Gruber, Ph.D
Director

Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993

Tel.: [redacted]
Email: [redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

To: File

From: Julia Tierney, JD, Acting Chief of Staff

Date: July 21, 2021

Re: July 19, 2021 Meeting with CBER regarding Review of Biologics License Application for Pfizer/BioNTech COVID-19 Vaccine

---

On July 19, 2021, Dr. Woodcock, Acting Commissioner of Food and Drugs, and I met with Dr. Peter Marks, Director, Center for Biologics Evaluation and Research (CBER), Dr. Marion Gruber, Director, Office of Vaccine Research and Review (OVRR) in CBER, and Dr. Philip Krause, Deputy Director, OVRR/CBER to discuss the process for review of the Biologics License Application (BLA) for the Pfizer/BioNTech COVID-19 Vaccine.

The meeting began with a discussion of the review process for BLAs in CBER in general and with respect to the Pfizer/BioNTech BLA. Dr. Woodcock asked questions about the structure and staffing of the BLA Review Committee, to which Dr. Gruber responded. Dr. Gruber stressed the complexity of the additional data generated after the EUA issuance that were submitted to the underlying IND, including safety data, and the need to have multiple experienced reviewers for disciplines such as medical officers and statisticians. Dr. Gruber referred to a memo she had provided to Dr. Marks regarding the anticipated timeframe to complete review of the BLA by September 15; Dr. Woodcock acknowledged that Dr. Marks had shared the memo. Dr. Gruber stated that she believed OVRR couldn't compress the review further. Dr. Woodcock asked question about any plans to leverage additional resources from other parts of the agency, such as consults from subject matter experts on CDER's computational science team or pediatric cardiologists in CDER and Commissioner's office. Dr. Gruber acknowledged that they had consulted with some staff in CDER, but not done so widely.

Dr. Krause reiterated many of Dr. Gruber's concerns, stressing that if the review is not thorough, it will further undermine vaccine confidence. He also described some of the additional data that had been submitted since issuance of the EUA, as well as other administrative steps that need to occur.

Dr. Woodcock thanked Dr. Gruber and Dr. Krause for their explanation of the issues associated with the BLA review and stressed the public health importance of this review, including the importance of performing a thorough review. She further stated that she is aware that Dr. Gruber has a [redacted] and will be out of the office for several weeks in July and August. Dr. Gruber acknowledged that she would be out of the office during this time and planned for Dr. Krause to be Acting Director of OVRR in her absence. Dr. Gruber raised that there may be political pressure at play.

Dr. Woodcock emphasized that she has not felt any political pressure, but feels the public health imperative associated with completing the review of the BLA and potentially have a licensed vaccine available. To this end, given the importance of this BLA, while Dr. Gruber is out of office, Dr. Woodcock explained, she is assigning Dr. Marks to lead on the Pfizer/BioNTech BLA, and Dr. Krause will be the Acting Director of OVRR and lead on all other files. Dr. Woodcock reiterated the public health need to complete this review. She will hold Dr. Marks accountable for completing the review as quickly as possible, while performing a thorough review that meets FDA's standards. Dr. Woodcock offered all of the resources of the Agency to get this done as timely as possible. Dr. Woodcock asked that Dr. Gruber transfer leadership of the BLA to Dr. Marks over the next week or two.

From: Marks, Peter [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=DFBB2B5BD38445CB9C9ADCA3F72DF53A-MARKSP]
Sent: 7/21/2021 2:25:03 PM
To: Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]; Gruber, Marion [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=019cd2669c7048f7a116d72b7682de44-gruber]
CC: Krause, Philip [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=00c6330fea0042fdb5571c3fdef792ed-krause]; Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]
Subject: RE: Your email on Review of Pfizer/BioNTech's BLA for Comirnaty, COVID-19 mRNA vaccine - Summary of meeting dated July 19 2021 - 8:30 am

Dear Marion,

I don't have much to add to Janet's response below, except to echo her gratitude for all of your work and to say that I remain absolutely committed to ensuring that we maintain our high quality standards in any work undertaken to further expedite the BLA review.

Thank you again.

Best Regards,
Peter

From: Woodcock, Janet [redacted]>
Sent: Wednesday, July 21, 2021 2:09 PM
To: Gruber, Marion [redacted].gov>
Cc: Krause, Philip [redacted]>; Marks, Peter [redacted]>; Tierney, Julia [redacted]
Subject: Re: Your email on Review of Pfizer/BioNTech's BLA for Comirnaty, COVID-19 mRNA vaccine - Summary of meeting dated July 19 2021 - 8:30 am

Dear Marion,

Thank you so much for your email. I appreciate you taking the time to speak on Monday, and appreciate you summarizing our conversation.

To begin with, let me express my sincere thanks for your leadership and for the hard work of the Office of Vaccines over the past year and half. Your efforts have made a tremendous difference in combating this pandemic.

It's clear that we are all in agreement about the public need to license the vaccine as soon as possible. This is a once in a lifetime public health crisis and probably the most important application we will all be involved in. With this public health imperative in mind, as well as the intensifying problem of vaccine hesitancy, we all also agree about the importance of not only reviewing this BLA as efficiently as possible, but also ensuring that it is done thoroughly and in keeping with FDA's high standards that protect and promote the public health. With respect to the specific timeline for completion that you propose, I do not have enough information to venture an opinion. I have asked Peter to become familiar with the details of the various elements of the review process and to work with the team to identify potential efficiencies, which they can report back to me during status updates. I also reiterate my offer to provide any resources that the Agency has to assist in components of the review.

Finally, Marion, I offer you and your family my best wishes.

Janet

From: Marks, Peter [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=DFBB2B5BD38445CB9C9ADCA3F72DF53A-MARKSP]
Sent: 7/20/2021 2:31:01 PM
To: Gruber, Marion [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=019cd2669c7048f7a116d72b7682de44-gruber]; Gottschalk, Laura [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9839a4146ef74943b3bd34fadcd29132-Laura.Gotts]; Naik, Ramachandra [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6f65ca32552f4cdab961dae0d4576981-NaikR]; Smith, Michael (CBER) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=22f70d8058734aca97200cc280820792-SmithM]; Prutzman, Kirk C [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=be2a535cd0e74125b89a712142e16dfb-PrutzmanK]; Sutkowski, Elizabeth M. [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c9c420dc83aa49e4b1adb0f70156fa08-sutkowski]; Wollersheim, Susan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=00541f26747c48c09d7b38f8968d3e0e-Susan.Wolle]; Lee, Lucia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c2d89bf8adec408fb3dd10c29d63d0fc-LeeL]; Allende, Maria [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e3eb3dba5ebf44aabac32aa1a5b58d83-ALLENDEM]; Cheung, Anissa [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5a5e55be048a4eb7ae6ccf49aa9e58b3-CheungA]; Peden, Keith [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bb98ff79baa14648856af0e912018b0c-peden]; Wang, Hsiaoling [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d2940f1d718047d1bc9845af576ba17e-WangH]; Yitbarek, Emnet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=be4b6baec6934430b62c24070d2502c8-Emnet.Yitba]; Garcia, Karla [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7187f0f732fb404493d20fa51cf246e1-Karla.Garci]; Choudhary, Anil [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=15945f881e8849b1a1addfa50fab83f6-ChoudharyA]; Alvarado, Esmeralda [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d23ee59ef3a04eaaba82cfcdd3afd5ce-Esmeralda.A]; Anderson, Marie [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4b8be33bb5c6478db7f097604e4d02e3-Marie.Ander]; Hulme, Cheryl [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5d842ca821194097ba71c3719c256317-hulme]; Pan, Tao [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6a44502b9b48454fa2283f9d30f904ce-PanT]; Kenney, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b1c6983472a7479fb24f45b232e8a344-Kenneyj]; Shahabuddin, Muhammad [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=284daf53421d455fae52a3ed30540074-shahabuddin]; Eichelberger, Maryna [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b0fa1c0f75154b1caca906c981fabb88-Eichelberge]; Quander III, Joseph [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=22607b68bc8d4427a7adcafcb87a318f-quander]; Al-Humadi, Nabil [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9683cea1300a4f739790dc8ad4eb6fbf-AlHumadiN]; Green, Martin (Dave) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c435014ab2a74b8792f882e802a41b4f-GREENM]; Huang, Lei [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=58ce4f4d0fc84e41b240cc839cc67bec-Lei.Huang]; Lin, Tsai-Lien [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fdc20f6b1b0d4699be88d5545366bfa9-Lints]; Thompson, Deborah

[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=3b1daeb32ffc4eb9ad43753eb1af30a2-Deborah.Tho]; Baumblatt, Jane
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=ebf078d94b9144178863a9180e4710dd-Jane.Baumbl]; Niu, Manette
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=ee2a4a5155724814a9836019691caba7-Manette.Niu]; Jones, Kathleen
(CBER) [/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=39f078595fe54c58963eccae13a653e8-Kathleen.Jo]; Fontan, Laura
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=254ab94e05104f5e89cd4ae937093214-Laura.Fonta]; Zubkova, Iryna
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=071581a38dba4163a1f28c5302c4df7d-Zubkova]; Li, Nicole
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=10ab585b56774813963d7e26a2383bee-Nicole.Li]; Peters, Lori
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=7371179937f7444b819ed7544004403c-PetersL]; Ertel, Donald
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=afdaa30818374edb81e0cfbb6e755290-ErtelD]; Chun, Haecin
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=634facb0ad7d40ac8ad0bab5bfc00561-ChunH]; Cato, Dennis
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=fe92b2ec026e40f9bf775df71458abd4-CatoD]; Elekwachi, Oluchi
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=b80042a0033b43a89d9f255db7d7cebf-ELEKWACHIO]; Stockbridge, Lisa L
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=be80d47bd2f342caa98a78594f2426cc-STOCKBRIDGE]; Sausville, Robert
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=514d822e2f744acb987245ae54ae9424-sausville]; Stewart, Daphne
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=acde59aa9c8b40fd9afa68feac730bc6-stewart]; Nelle, Timothy
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=a9a8620f04014ce4b6420f1f599a9117-Nelle]; Schwab, David
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=0eac57a473824c91acc30137a6c44a85-SchwabD]; Baldwin, Brenda
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=5fb1847133af492da626a7240e1db5fc-Baldwin]; Price, Gregory
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=480f4099d2fa4e10be0cb2fa32376baa-PriceG]; Wu, Zhongren
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=c143154833c1455a981439187748dcc3-Zhongren.Wu]; Jones, Dana
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=7765564e42f0491992b22379a1e3d771-MartinDa]; Schwartz, Ann T
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=dd85358364f54b2d9f823d3f79ab7f2e-SchwartzA]; Allen, Ekaterina
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=83070c40d3324f1a95f458067da7a01c-Ekaterina.A]; Tang, Xinyu
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=81044057bca044c0b8080a865507cd08-Xinyu.Tang]; Yang, Ye
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=64dd48cb8d35427c9cd0a14a1cecfb48-Ye.Yang]

CC: Crim, James [/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=e3793abc329a4f0f8faee12d3204ff5c-CrimJ]; McVittie, Loris
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=dad145be676748898016f37b0760bc61-mcvittie]; Fink, Doran
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=b3bfbf3e7bea40b1b726937796eba4e8-FinkDo]; Pratt, Douglas R.
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=682a5e028a4e428aa16bc3c206518d81-prattd]; Weir, Jerry P.

[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=5d220ee1a49746899d88fd8077e08486-Weirj]; Levis, Robin
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=d09daa7be5da44d983b8436c0ecf01b5-levis]; Eltermann, John
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=c9ddc6c10cfe4f81a9fb73b478a77d46-eltermann]; Scott, John
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=91620658ce0243e38241d198be1a5461-ScottJ]; Lee, Shiowjen
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=518ddcec072b472d9e106e77e211a8b9-SHL]; Nair, Narayan
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=debe49605be845e5a44d59cf099b8cb8-Narayan.Nai]; Alimchandani, Meghna
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=963019bc771f43cfb664c1729aaf5a17-Meghna.Alim]; Renshaw, Carolyn
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=3059e1f9a9104fd78831f6e2d8f6e13d-RENSHAW]; Mampilly, Carrie
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=162b1c8729d64723bbed003422a69f25-CYamamur]; Krause, Philip
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=00c6330fea0042fdb5571c3fdef792ed-krause]; Roberts, Jeff
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=f99ba866ca234f6d826007b9f1429e8e-RobertsJ]; Finn, Theresa
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=7dd823be93eb40699e01c5a370b871cc-finn]; Farizo, Karen
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=a4e44a6d3b754a66ad321c00f9b1debd Farizo]; Izurieta, Hector
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=2dde96468af24b2d9ef03b853eeb3af9 Izurieta]; Hess, Maureen
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=23ed9c01196f4765b89921c357f855f9-Hessma]; Cho, David S (CBER)
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=d47af9d991af4c1fbf7cb4c1d287f83e-ChoD]; Devore, Nicolette
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=4cd9d011e02c45d6b1005d46342cad69-Devore]; Walinsky, Sarah
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=97a2ad6b3c4549a78542fce1a086f7ea-Sarah.Walin]; Witten, Celia (CBER)
[/o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=fc08ebb3ac61486da9f1b4046757c5cf-Witten]

Subject: RE: Pfizer BLA COVID-19 vaccine

Dear BLA Review Team Members,

First and foremost, I want to thank Dr. Gruber for her incredible leadership facilitating the development and review of COVID 19 vaccines and other products during this pandemic. [redacted] Second, I want to thank all the members of the [redacted] teams who have been tirelessly reviewing the various COVID-19 files for your amazing efforts.

During Dr. Gruber's [redacted] I look forward to working with all of you to ensure that we continue the thorough evaluation of manufacturing quality, safety and effectiveness for the Pfizer vaccine that has been ongoing, while doing our best to expedite this process with the ultimate goal of helping to save as many additional lives as possible through the availability of a licensed vaccine that reflects the quality work that defines us. With the pandemic appearing to enter a new phase, it is critical that we take a careful look at whether there any efficiencies we can gain in the review process, or additional resources that can be leveraged, to complete the review as efficiently as possible while maintaining the high standards on which the public relies.

The virtual door to my office is always open, so please feel free to be in touch with questions or concerns. I look forward to meeting as a team later this week.

Best Regards,
Peter

From: Gruber, Marion <[redacted]>
Sent: Tuesday, July 20, 2021 12:27 PM
To: Gottschalk, Laura <[redacted]; Naik, Ramachandra [redacted]>; Smith, Michael (CBER) [redacted]>; Prutzman, Kirk C <[redacted]>; Sutkowski, Elizabeth [redacted]; Wollersheim, Susan <[redacted]>; Lee, Lucia [redacted]>; Allende, Maria <[redacted]>; Cheung, Anissa [redacted] Peden, Keith <[redacted]>; Wang, Hsiaoling <[redacted]>; Yitbarek, Emnet <[redacted]; Garcia, Karla [redacted] Choudhary, Anil [redacted]; Alvarado, Esmeralda [redacted] Anderson, Marie [redacted]; Hulme, Cheryl [redacted]; Pan, Tao [redacted] Kenney, James [redacted]; Shahabuddin, Muhammad [redacted] Eichelberger, Maryna [redacted] III, Josep[redacted] Al-Humadi, Nabil [redacted]; Green, Martin (Dave) [redacted] Huang, Lei [redacted] Lin, Tsai-Lien [redacted] Thompson, Deborah [redacted]; Baumblatt, Jane [redacted], Manette [redacted]; Jones, Kathleen (CBER) [redacted] Fontan, Laura [redacted] Zubkova, Iryna <[redacted]; Li, Nicole <[redacted] Peters, Lori [redacted]; Ertel, Donald <[redacted]>; Chun, Haecin <[redacted]; Cato, Dennis [redacted]; Elekwachi, Oluchi [redacted]; Stockbridge, Lisa L [redacted]; Sausville, Robert [redacted] Stewart, Daphne [redacted]>; Nelle, Timothy <[redacted] Schwab, David [redacted]; Baldwin, Brenda [redacted] Price, Gregory [redacted]; Wu, Zhongre[redacted] Jones, Dana <[redacted]; Schwartz, Ann T [redacted]; Allen, Ekaterina [redacted]>; Tang, Xinyu [redacted]>; Yang, Ye <[redacted]
Cc: Crim, James [redacted]gov>; McVittie, Loris <[redacted]>; Fink, Doran [redacted] Pratt, Douglas R <[redacted] Weir, Jerry P [redacted] Levis, Robin <[redacted]>; Eltermann, John <[redacted]>; Scott, John [redacted]>; Lee, Shiowjen <S[redacted] Nair, Narayan <[redacted] Alimchandani, Meghna [redacted] Renshaw, Carolyn [redacted]; Mampilly, Carrie [redacted] Gruber, Marion [redacted] Krause, Philip [redacted] Finn, Theresa [redacted] Farizo, Karen [redacted]>; Izurieta, Hector [redacted]>; Hess, Maureen [redacted] Marks, Peter [redacted]; Cho, David S (CBER) [redacted] Devore, Nicolette [redacted]
Subject: Pfizer BLA COVID-19 vaccine

Dear review committee and supervisors,

First, let me thank you for your tireless efforts in expediting your thorough review of the BLA for Pfizer's COVID-19 mRNA vaccine. This is a complex BLA and it is important that we conduct a thorough evaluation of the safety, effectiveness and manufacturing data submitted with this application. I know that review efforts in the various disciplines are ongoing and that excellent progress is being made. Our target date for taking regulatory action is September 15. As you know, I will be taking some [redacted] While I am gone, at the directive of the Acting Commissioner, OVRR management and oversight of this BLA will be delegated to Dr. Marks and Dr. Krause will be overseeing other regulatory

and programmatic activities in OVRR. Dr. Marks and I will be meeting with you prior to the end of this week to answer your questions and he will inform you of his expectations. I am confident that you will continue your review efforts to facilitate and expedite the licensure of this vaccine so critical to public health.

Sincerely,
Marion

Marion F. Gruber, Ph.D
Director

Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993

Tel.: [redacted]
Email: [redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

BLA STN 125742/0
BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)
COMIRNATY (COVID-19 mRNA Vaccine)

Review activities and target completion dates

Task title/description/milestone	**Target completion date (Week of…)**
BLA submission Roll 1 submission Roll 2 submission (final	 May 6, 2021 May 18, 2021
Received	May 18, 2021
Committee assignment	May 19, 2021
First Committee Meeting	June 3, 2021
Discussion of testing of DS and DP to support licensure (DVP and DBSQC)	June 4, 2021
Filing review complete	June 23, 2021
Request for lot release protocol template, reagents and samples for testing	June 25, 2021
Filing Meeting	June 29, 2021
Proprietary Name Review complete	July 2, 2021
Reagents and samples received	July 9, 2021
Filing Action	July 15, 2021
VRBPAC meeting	No plan to hold an advisory committee meeting
Pre-licensure facilities inspections complete	July 23, 2021
PeRC briefing materials due	July 27, 2021
Post-authorization safety/Epidemiology/ Pharmacovigilance Plan review memo complete	August 5, 2021
PeRC meeting	August 10, 2021
First set of comments on Package Insert	August 11, 2021
Notification of PMC/PMR	August 13, 2021
Obtain Lot Release Clearance	August 16, 2021
Obtain Compliance check	August 16, 2021
Determine non-proprietary name	August 16, 2021
APLB review memo complete	August 20, 2021
Comments on carton and container labels	August 20, 2021
Establishment Inspection Reports complete	August 27, 2021
Establish product expiry date	August 30, 2021
Nonclinical review memo complete	August 30, 2021
DMPQ memo complete	August 30, 2021
Waiver for FDA-designated suffix to proper name	August 30, 2021
Lot release protocol and testing plan finalized	August 30, 2021
CMC review memo complete	August 30, 2021
Clinical review memo complete	August 30, 2021
Statistical review memo complete	August 30, 2021

BLA STN 125742/0 Review activities and target completion dates

BIMO review memo complete	August 31, 2021
Mid-Cycle Meeting, Internal (scheduled)	August 31, 2021
DBSQC review memo complete	September 3, 2021
Carton and container labels done	September 3, 2021
Labeling review complete	September 10, 2021
SBRA complete (Draft: August 13, 2021)	September 10, 2021
Mid-Cycle Communication (scheduled)	September 13, 2021 (may be canceled)
Target Action Due Date	**September 15, 2021**
DS and DP testing complete (DBSQC)	After the ADD

Dr. Gruber asked if Dr. Woodcock agreed with the target review date of September 15, 2021 and Dr. Woodcock replied that she would like Dr. Marks to review the status of the file and talk to the team to determine if there is a way to move forward more quickly.

Dr. Gruber stated that she has full confidence in the review team moving forward, as well as Dr. Krause's leadership. Dr. Gruber indicated that the processes in place are well established and that her planned leave wouldn't affect that. She acknowledged Dr. Woodcock's decision to assign leadership of the review to Dr. Marks, but did not agree with it.

Dr. Woodcock stated that she had no doubt about the dedication of the review team or the competence of Dr. Krause as a leader. She indicated that, given the public health priority of this application, she wants as many eyes as possible on this application and wants Dr. Marks to lead this review. She will be asking for briefings on the review, including any issues identified such as potential neurological or cardiological side effects. Dr. Woodcock emphasized that she maintains an open door policy.

Dr. Woodcock again reiterated that she would like Dr. Gruber to work very closely with Dr. Marks to make sure he understands who is doing what and if there are potentially rate limiting steps, such as clinical review, that they are identified and addressed.

From: Marks, Peter [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=DFBB2B5BD38445CB9C9ADCA3F72DF53A-MARKSP]
Sent: 8/23/2021 1:57:14 PM
To: Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]
Subject: RE: you ok with this?

Dear Julie,

I am fine with this language.

Best Regards,
Peter

From: Tierney, Julia [redacted]
Sent: Monday, August 23, 2021 1:44 PM
To: Marks, Peter [redacted]
Subject: you ok with this?

The FDA-approved Pfizer-BioNTech product COMIRNATY (COVID-19 Vaccine, mRNA) and the FDA-authorized Pfizer-BioNTech COVID-19 Vaccine under EUA have the same formulation and can be used interchangeably to provide the COVID-19 vaccination series without presenting any safety or effectiveness concerns. Therefore, providers can use doses distributed under EUA to administer the vaccination series **as though it is the licensed vaccine. For purposes of administration, doses distributed under the EUA are interchangeable with the licensed doses**. The Fact Sheet for Recipients provides additional information about both the approved and authorized vaccine. Providers should continue to use the vaccines on their shelves.

Julia C. Tierney, JD (she/her)
Acting Chief of Staff

U.S. Food and Drug Administration
(301) 796-8602 (office) (forwarded)
[redacted] (cell)
[redacted]v

FDA U.S. FOOD & DRUG ADMINISTRATION

DATE: August 13, 2021

FROM: Haecin Chun, MS, Bioresearch Monitoring Branch (BMB)
Division of Inspections and Surveillance (DIS)
Office of Compliance and Biologics Quality (OCBQ)

THROUGH: Dennis Cato, Chief BMB

THROUGH: Carrie Mampilly, MPH, Director DIS

THROUGH: Mary A. Malarkey, Director OCBQ

TO: Ramachandra Naik, PhD, Chair
Susan Wollersheim, MD, Clinical Reviewer
CAPT Ann Schwartz, MD, Clinical Reviewer
CAPT Michael Smith, PhD, RPM
Laura Gottschalk, PhD, RPM

SUBJECT: Bioresearch Monitoring (BIMO) Discipline Review Memo
SPONSOR: BioNTech Manufacturing GmbH
PRODUCT: COVID-19 Vaccine, mRNA (COMIRNATY)
BLA: STN 125742/0

FINAL SUMMARY STATEMENT

BIMO inspection assignments were issued for a total of nine (9) clinical study sites that participated in the conduct of Study Protocol C4591001. Three (3) of these inspection assignments focused on clinical study sites that enrolled the pediatric population and six (6) of the study sites enrolled the adult population. The inspections did not reveal findings that impact the Biologics License Application (BLA).

BACKGROUND

On February 4, 2020, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency (PHE) involving to a novel coronavirus named SARS-CoV-2 that causes Coronavirus Disease 2019 (COVID-19). On March 27, 2020, the Secretary of HHS issued a Notice of Emergency Use Authorization (EUA) Declaration pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or the Act).

In response to the PHE, BIMO reviewers proactively performed a review of the sponsor's investigational new drug application (IND 19736) and issued the necessary BIMO inspections to review the study conduct of Protocol C4591001, "*A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals*."

Protocol C4591001 was a multi-center study conducted at a total of 153 clinical sites: 131 study sites in the United States and 22 sites outside of the United States. Due to the COVID-19 pandemic travel restrictions, only the domestic sites were considered for an on-site BIMO inspection. Initially, six (6) study sites were inspected, before FDA issued the original Emergency Use Authorization for individuals 16 years of age and older. Subsequently, three (3) additional sites were inspected before FDA authorized use of the vaccine in those 12 and older. All of the study sites were selected based on subject enrollment, previous inspectional history, and other information submitted in IND 19736.

The inspections were conducted in accordance with FDA's Compliance Program 7348.811, Inspection Program for Clinical Investigators, focusing primarily on the study conduct, human subject protection and compliance with related FDA regulations. The data integrity and verification portion of the BIMO inspections were limited because the study was ongoing, and the data required for verification and comparison were not yet available to the IND. The table below summarizes the domestic study site information and the outcome of each BIMO inspection:

Site ID	Site Location	Form FDA 483 Issued	Final Classification
1007	Cincinnati Children's Hospital Medical Center Cincinnati Center for Clinical Research Cincinnati, OH	No	No Action Indicated (NAI)
1009	J. Lewis Research Inc./ Foothill Family Clinic South, Salt Lake City, UT	No	NAI
1044	Virginia Research Center, LLC. Midlothian, VA	No	NAI
1056	Indago Research and Health Center, Inc. Hialeah, FL	No	NAI
1109	Deland Clinical Research Unit DeLand, FL	No	NAI
1118	Meridian Clinical Research, LLC. Binghamton, NY	No	NAI
1125	Meridian Clinical Research, LLC Norfolk, NE	No	NAI
1133	Research Centers of America Hollywood, FL	No	NAI
1149	Collaborative Neuroscience Research, LLC at two locations: Long Beach & Garden Grove, CA	No	NAI

SIGNIFICANT INSPECTIONAL FINDINGS
No significant inspectional findings were noted.

SPONSOR/MONITORING ISSUES
No significant sponsor or monitoring issues were noted at the sites that were inspected.

FINANCIAL DISCLOSURE
The Clinical Investigator Compliance Program directs the FDA investigator to ask the clinical investigator if and when he/she disclosed information about his/her financial interests to the sponsor and/or interests of any sub-investigators, spouse(s) and dependent children, and if and when the information was updated. The information submitted to the BLA was verified for each of the inspected clinical sites.

ADMINISTRATIVE FOLLOW-UP
Should you have any questions or comments about the contents of this memo or any aspect of Bioresearch Monitoring, please contact me at 240-402-8038.

Haecin Chun
Consumer Safety Officer

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

CBER SENTINEL PROGRAM SUFFICIENCY MEMORANDUM

From:	Joyce Obidi Health Scientist, CBER Surveillance Program Office of Biostatistics and Epidemiology (OBE)
Through:	Hui-Lee Wong Associate Director, CBER Surveillance Program, OBE
Subject:	CBER Sentinel Program Sufficiency Assessment
Product:	COMIRNATY; BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)
Sponsor:	Pfizer
STN:	125742/0
Proposed Indication:	Active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals ≥16 years of age.
Approval Type:	☒ Priority ☐ Standard review
Submission Date:	May 18, 2021
Action Due Date:	January 16, 2022

1. Objectives/Scope:

This memo reviews the capability and sufficiency of the CBER active post-market risk identification and analysis system referred to as the CBER Sentinel Program to evaluate the serious risk for myocarditis and pericarditis following receipt of BNT162b2, a COVID-19 Vaccine indicated for active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals ≥16 years of age in lieu of a safety post-market requirement (PMR) study under FDAAA[1]. The CBER Sentinel Program covers activities conducted through the contract with the Harvard Pilgrim Health Care Institute, the current and future contracts through the Biologics Effectiveness and Safety (BEST) Initiative, and the interagency agreement with the Centers for Medicare and Medicaid (CMS). Please see the STN 125742/0 OBE/Division of Epidemiology (DE) review of the Pharmacovigilance Plan (PVP) for background on the serious risks of myocarditis and pericarditis, and subclinical myocarditis. Post-authorization safety data identified serious risks for myocarditis and pericarditis after COMIRNATY, with increased risk in males under 30 years of age, particularly following the second dose, and onset of symptoms within 7 days following vaccination. At the end of May 2021 CDC issued clinical considerations regarding myocarditis and pericarditis after receipt of mRNA COVID-19 vaccines among adolescents and young adults (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html). The topic was presented and discussed at the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting on June 10, 2021 and the Advisory Committee for Immunization Practices (ACIP) meeting on June 23, 2021. The Emergency Use Authorization (EUA) Fact Sheet was revised on June 25, 2021 to add a Warning for myocarditis and pericarditis. A postmarketing observational safety study(ies) is needed to assess myocarditis and pericarditis following administration of COMIRNATY (BNT162b2) to:

a. Quantify the magnitude of risk by age, sex, and dose
b. Follow up cases for recovery status and long-term sequelae
c. Characterize subclinical cases of myocarditis

2. CBER Sentinel Program Sufficiency Assessment:

Determination of the sufficiency of the CBER Sentinel Program to further characterize the serious risk of myocarditis and pericarditis with BNT162b2 was based on the following factors:

[1] Under section 901 of the Food and Drug Administration Amendments Act (FDAAA), "*The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B).*"NOTE: The active post-market risk identification and analysis system under subsection (k)(3) refers to the Sentinel program.

[2] ISBT 128 is a global standard for the safe identification, accurate labeling, and efficient information transfer of medical products of human origin (including blood, cells, tissues, milk, and organ products) across disparate national and international health care systems. https://www.iccbba.org/isbt-128-basics

2.1 Identification of exposure to BNT162b2

2.2 Identification of the appropriate study population: Patients ≥ 16 years of age

2.3 Characterization of occurrence of myocarditis and pericarditis, and subclinical myocarditis, with BNT162b2

2.4 Identification of exposure to comparator product (when applicable)

2.1 Assessment for identification of exposure to BNT162b2

2.1.1. Is the CBER Sentinel Program able to identify the product (exposure) of interest?

Please answer each question i – xi, including sub-questions.		Yes	No
i.	Is this the first or the only FDA-approved product for the indication?	☒	☐
ii.	Can the exposure be identified using a billing or reimbursement coding system? *If yes, check all that apply:* ☒ *CPT* ☒ *HCPCS* ☒ *NDC* ☐ *ICD* ☐ *Other: [Coding system]*	☒	☐
iii.	Is the ISBT 128 coding system needed for the product identification?	☐	☒
iv.	Can the reimbursement code of the product identify the brand name?	☒	☐
v.	Is a history of uptake for previously approved products for the same indication needed? *If yes, list all products:*	☐	☒
vi.	Is medical chart review needed to identify or validate the identification of this product?	☐	☒
vii.	Are claims data sources needed for exposure identification?	☒	☐
viii.	Are electronic health record (EHR) data sources needed for exposure identification?	☐	☒
ix.	Are any other health record type data sources needed for exposure identification? *If yes, all health record types needed: [e.g., Registries, any other health records]*	☒	☐
x.	Is product lot number needed for identification of this product?	☐	☐
xi.	Is there a care setting of interest required for identification of this product? *If yes, check all that apply:* ☐ *Inpatient* ☐ *Outpatient* ☐ *Emergency Room* ☐ *Other: Hospitalization*	☐	☒

2.1.2. Summary for product exposure identification

☒ Available data sources in the CBER Sentinel Program are *sufficient to identify the exposure of the product* BNT162b2 *due to reasons identified in* 2.1.1.ii. Billing codes for BNT162b2 allows for clear ascertainment of exposure to the product.

☐ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the exposure of the product [name]* due to reasons identified in [list all bullets from 2.1.1.i.—2.1.1.xi. that support insufficiency].

2.2. Assessment for identification of the appropriate study population: Patients ≥ 16 years of age

2.2.1. Is the CBER Sentinel Program able to identify the study population of interest?

Please provide an answer for each question i – vi, including sub-questions.		Yes	No
i.	Does age need to be identified? *If yes, list the inclusion and exclusion criteria.. Check all that apply for the level of granularity in ☐ Days ☐ Months ☒ Years*	☒	☐
ii.	Does sex need to be identified? *If yes, list the inclusion [List the sex to be included] and exclusion criteria [List the sex to be excluded].*	☐	☒
iii.	Does race need to be identified? *If yes, list the inclusion [List race to be included] and exclusion criteria [List race to be excluded]*	☐	☒
iv.	Can the study population be identified in the data sources required for the exposure and outcome identification?	☒	☐
v.	Was this population previously identified within the CBER Sentinel Program activities?	☒	☐
vi.	Is there a requirement for linking mothers to their newborns in the data sources?	☐	☒

2.2.2. Summary for identification of study population

☒ Available data sources in the CBER Sentinel Program are *sufficient to identify the study population of interest*, patients > 16 years of age, due to reasons identified in 2.2.1.i - 2.2.1.vi. This study population of interest has been identified in the data sources required of exposure (BNT162b2) and outcome (myocarditis/pericarditis).

☐ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the study population of interest* due to reasons identified in [list all bullets from 2.2.1.i.—2.2.1.vi. that support insufficiency].

2.3 Assessment for characterization of occurrence of myocarditis and pericarditis, and subclinical myocarditis

2.3.1 Is the CBER Sentinel Program able to identify the outcome(s) of interest?

Please provide an answer for each question i – xi, including sub-questions.		Yes	No
i.	Can the outcome of interest be identified using a billing or reimbursement coding system? If yes, *check all that apply:* ☒ *ICD* ☐ *CPT* ☐ *Other: Medical Record Review*	☒	☐
ii.	Are there surrogate data elements or biomarkers that can assist to identify the outcome of interest? *If yes, check all that apply:* ☐ *Laboratory Test Results* ☐ *Prescription drug* ☐ *Order of lab test* ☐ *Order of other diagnostic modalities* ☐ *Other: [Data element/Biomarker]*	☐	☒
iii.	Are there specific care settings in which this outcome is identified? *If yes, check all that apply:* ☒ *Inpatient* ☒ *Outpatient* ☒ *Emergency Room* ☒ *Other: Hospitalization*	☒	☐
iv.	Was this outcome previously identified within the CBER Sentinel Program activities? *If yes, in what population was it used? It was used in a similar population of Medicare beneficiaries 65y and older.*	☒	☐
v.	Is there a validated and acceptable algorithm available in the literature to identify the outcome of interest? *If yes, list the PPV [PPV] and describe the population in which it was validated:*	☐	☒
vi.	Is a minimum follow-up time needed to identify the outcome of interest? *If yes, what is the required follow-up period? 3-6 months*	☒	☐
vii.	Is medical chart review required to identify or validate the identification of the outcome?	☒	☐
viii.	Is the prevalence of the outcome known? *If yes, list background rates. 0.95-2/16 per 100,000 PY in Gubernot 2021*	☒	☐
ix.	Are claims data sources needed for outcome characterization?	☒	☐
x.	Are electronic health record (EHR) data sources needed for outcome characterization?	☒	☐
xi.	Are any other health record type data sources needed for outcome characterization? *If yes, all health record types needed: Registries*	☒	☐

2.3.2 Summary of outcome characterization

☒ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the outcomes of* myocarditis and pericarditis due to reasons identified in 2.3.1.vi.—2.3.1.viii. Based on the prevalence of background rates estimated in the CBER Sentinel data sources and the number of observed myocarditis/pericarditis events in the CBER Sentinel Program on-going near-real time surveillance, the CBER Sentinel data sources are currently not sufficiently powered to assess the magnitude of risk for the 12-30 years old that has been reported in VAERS in an epidemiology study (e.g., self-controlled analyses). CBER Sentinel will continue to monitor these safety outcomes. In order to follow up cases for recovery status and long-term sequelae, a minimum follow up time of 3-6 months is required. CBER Sentinel data sources do not have sufficient longitudinal data on patients to conduct this type of analysis. Additionally, a study of subclinical myocarditis using CBER Sentinel data sources is not feasible because of the absence of a definition of subclinical myocarditis and unknown background incidence of troponin abnormalities.

2.4. Assessment for identification of exposure to comparator product (when applicable): NOT APPLICABLE

2.4.1. Is the CBER Sentinel Program able to identify the required comparator product? Respond to the questions below, if applicable.

Please provide an answer for each question i – xi, including sub-questions		Yes	No
i.	Is a comparator product needed for the assessment? ***If no, skip to section III for Recommendation***. *If yes, list all products.*	☐	☐
ii.	Can the comparator product be identified using a billing reimbursement code? *If yes, check all that apply: ☐ CPT ☐ HCPCS ☐ NDC ☐ ICD ☐ Other: [Billing reimbursement code]*	☐	☐
iii.	Can the comparator product be exclusively identified using the billing reimbursement codes?	☐	☐
iv.	Is the ISBT 128 coding system[2] needed for the comparator product identification?	☐	☐
v.	Can the reimbursement code of the comparator product identify the brand name?	☐	☐
vi.	Is medical chart review needed to identify or validate the identification of this comparator product?	☐	☐
vii.	Are claims data sources needed for exposure identification of the comparator product?	☐	☐
viii.	Are electronic health record (EHR) data sources needed for exposure identification of the comparator product?	☐	☐

Please provide an answer for each question i – xi, including sub-questions		Yes	No
ix.	Are any other health record type data sources needed for exposure identification of the comparator product? *If yes, list all health record types needed: [e.g., Registries, any other health records]*	☐	☐
x.	Is product lot number needed for identification of this comparator product?	☐	☐
xi.	Is there a care setting of interest for identification of this comparator product? *If yes, check all that apply:* ☐ *Inpatient* ☐ *Outpatient* ☐ *Emergency Room* ☐ *Other: Hospitalization*	☐	☐

2.4.2. Summary for comparator exposure identification

☐ Available data sources in the CBER Sentinel Program are *sufficient to identify the comparator product* due to reasons identified in [list all bullets from 2.4.1.i.—2.4.1.xi. that support sufficiency].

☐ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the comparator product* due to reasons identified in [list all bullets from 2.4.1.i.—2.4.1.xi. that support insufficiency].

3. Recommendation:

☐ The CBER Sentinel Program is *sufficient* to assess the serious risk of [describe] associated with [product] at this time. [Summarize all bullets 2.1.—2.4. that support sufficiency]

☒ The CBER Sentinel Program is NOT sufficient to assess the serious risks of myocarditis and pericarditis, and subclinical myocarditis associated with COMIRNATY (BNT162b2) in lieu of PMR safety studies under FDAAA. At the time of BLA approval, the data sources in the CBER Sentinel Program are not sufficient to identify the outcomes due to lack of sufficient power to assess the magnitude of risk in patients 12-30 years of age. In addition, CBER Sentinel Program is not sufficient to follow up cases for recovery status and long-term sequelae, or for identification and characterization of subclinical myocarditis cases.

From: Sly, Elizabeth
To: Sly, Elizabeth
Subject: FW: Request for as meeting
Date: Tuesday, March 7, 2023 5:46:37 PM
Attachments: image001.png

From: Gruber, Marion <[redacted]>
Sent: Friday, August 13, 2021 6:29 PM
To: Marks, Peter [redacted]
Subject: RE: Request for as meeting

Dear Peter,
Next Thursday at noon works! see you then.
Marion

From: Marks, Peter <[redacted]>
Sent: Friday, August 13, 2021 3:41 PM
To: Gruber, Marion [redacted]>
Subject: RE: Request for as meeting

Dear Marion,

No problem. I was planning on being at FDA starting late morning on Thursday. Could noon on Thursday work for you?

In the meantime, I hope that [redacted]

Your team in vaccines is amazing.

Best Regards,
Peter

From: Gruber, Marion <[redacted]>
Sent: Friday, August 13, 2021 2:21 PM
To: Marks, Peter [redacted]
Subject: Request for as meeting

Dear Peter,
Are you planning to be at the WO campus next week? I would like to talk to you and I would prefer an in-person meeting if at all possible.
Please let me know and I will schedule around your availability.
Thanks,
Marion

Marion F. Gruber, Ph.D
Director

Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration, DHHS
10903 New Hampshire Ave.
Building 71, Rm. 3230
Silver Spring, Maryland 20993

Tel.: [redacted]
[redacted]

From: Sly, Elizabeth
To: Sly, Elizabeth
Subject: FW: Retirements
Date: Tuesday, March 7, 2023 5:47:11 PM

From: Krause, Philip <[redacted]
Sent: Monday, August 30, 2021 7:40 AM
To: Marks, Peter[redacted]
Cc: Gruber, Marion <[redacted]
Subject: Retirements

Hi Peter,

Marion mentioned over the weekend that she told you about her plans. I wanted to urgently provide you with information that I suspect will be useful for you going forward. I would have preferred to see you in person for this— but I also don't want to cause unnecessary delays as you make plans for the Office.

I am in a very similar position to Marion. [redacted] the public health crisis and the opportunity to make a big difference [redacted] — and I am very proud to have been part of the amazing work that OVRR has done. However, we've now accomplished some of the more complex public health and regulatory goals and I am [redacted] I have been planning to [redacted]

So I am writing to let you know formally that I will also retire as of [redacted] I know that this will be a tough time for the Office, and am ready to help with the transition in any way possible.

I'm dealing with [redacted] but would be happy to talk about the situation after that if you would like to.

Best regards,
Phil

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 4

1. EXECUTIVE SUMMARY 5

1.1 Demographic Information: Subgroup Demographics and Analysis Summary 7
1.2 Patient Experience Data 8

2. CLINICAL AND REGULATORY BACKGROUND 9

2.1 Disease or Health-Related Condition(s) Studied 9
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) 10
2.3 Safety and Efficacy of Pharmacologically Related Products 11
2.4 Previous Human Experience with the Product (Including Foreign Experience) 12
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 13
2.6 Other Relevant Background Information 14

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES 14

3.1 Submission Quality and Completeness 14
3.2 Compliance With Good Clinical Practices And Submission Integrity 15
3.3 Financial Disclosures 15

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 16

4.1 Chemistry, Manufacturing, and Controls 16
4.2 Assay Validation 16
4.3 Nonclinical Pharmacology/Toxicology 16
4.5 Statistical 16
4.6 Pharmacovigilance 16
4.7 Risk-Benefit Assessment 17

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW 18

5.1 Review Strategy 18
5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review 19
5.3 Overview of Clinical Studies 20
5.4 Consultations 21
5.4.1 Advisory Committee Meeting 21
5.5 Literature Reviewed 21

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS 23

6.1 Study C4591001 23
6.1.1 Objectives and Endpoints 24
6.1.2 Design Overview 24
6.1.3 Population 26
6.1.4 Study Treatments or Agents Mandated by the Protocol 27
6.1.5 Directions for Use 27
6.1.6 Sites and Centers 27
6.1.7 Surveillance/Monitoring 27
6.1.8 Endpoints and Criteria for Study Success 29
6.1.9 Statistical Considerations & Statistical Analysis Plan 30
6.1.10 Study Population and Disposition 31
6.1.11 Efficacy Analyses 43
6.1.12 Safety Analyses 56
6.1.13 Study Summary and Conclusions 81

6.2 Study BNT162-01 82

7. INTEGRATED OVERVIEW OF EFFICACY 83

8. INTEGRATED OVERVIEW OF SAFETY 83

9. ADDITIONAL CLINICAL ISSUES 83

9.1 Special Populations 83
9.1.1 Human Reproduction and Pregnancy Data 83
9.1.2 Use During Lactation 85
9.1.3 Pediatric Use and PREA Considerations 85
9.1.4 Immunocompromised Individuals 85
9.1.5 Geriatric Use 86
9.1.6 Patients with Human Immunodeficiency Virus (HIV) Infection 86

10. CONCLUSIONS 92

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS 94

11.1 Risk-Benefit Considerations 94
11.2 Risk-Benefit Summary and Assessment 98
11.3 Discussion of Regulatory Options 100
11.4 Recommendations on Regulatory Actions 101
11.5 Labeling Review and Recommendations 101
11.6 Recommendations on Postmarketing Actions 101

APPENDIX A CHARLSON COMORBIDITY INDEX 103

APPENDIX B CARDIAC DISORDERS FROM DOSE 1 TO DATE OF UNBLINDING AMONG PHASE 2/3 PARTICIPANTS 16 YEARS OF AGE AND OLDER 104

APPENDIX C DEATH NARRATIVES 106

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 [redacted]

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.

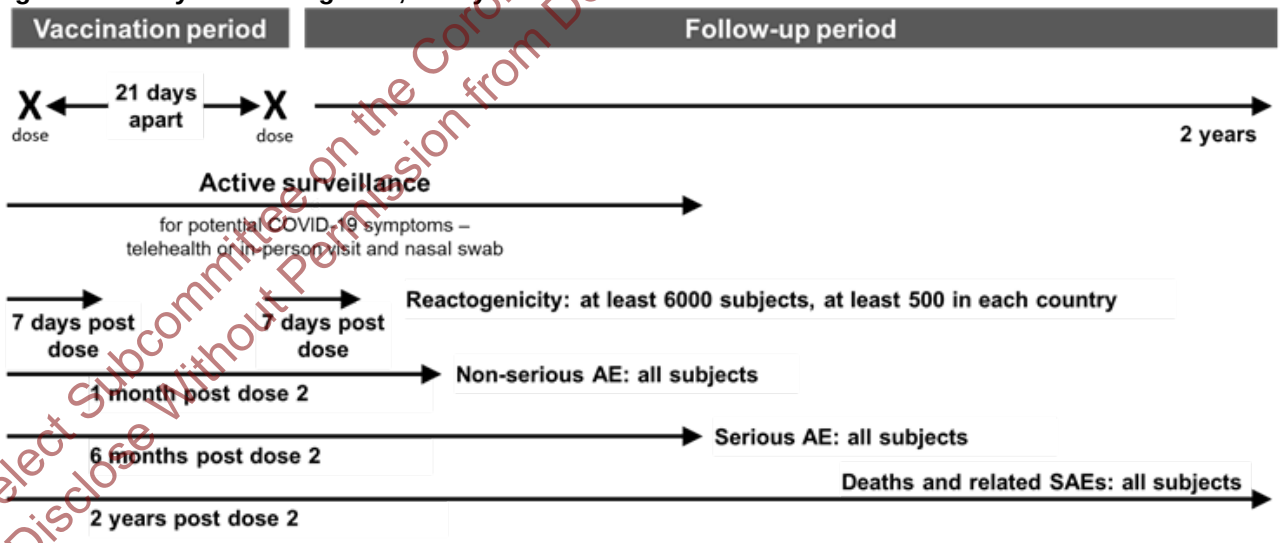
Safety

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 θ = 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.

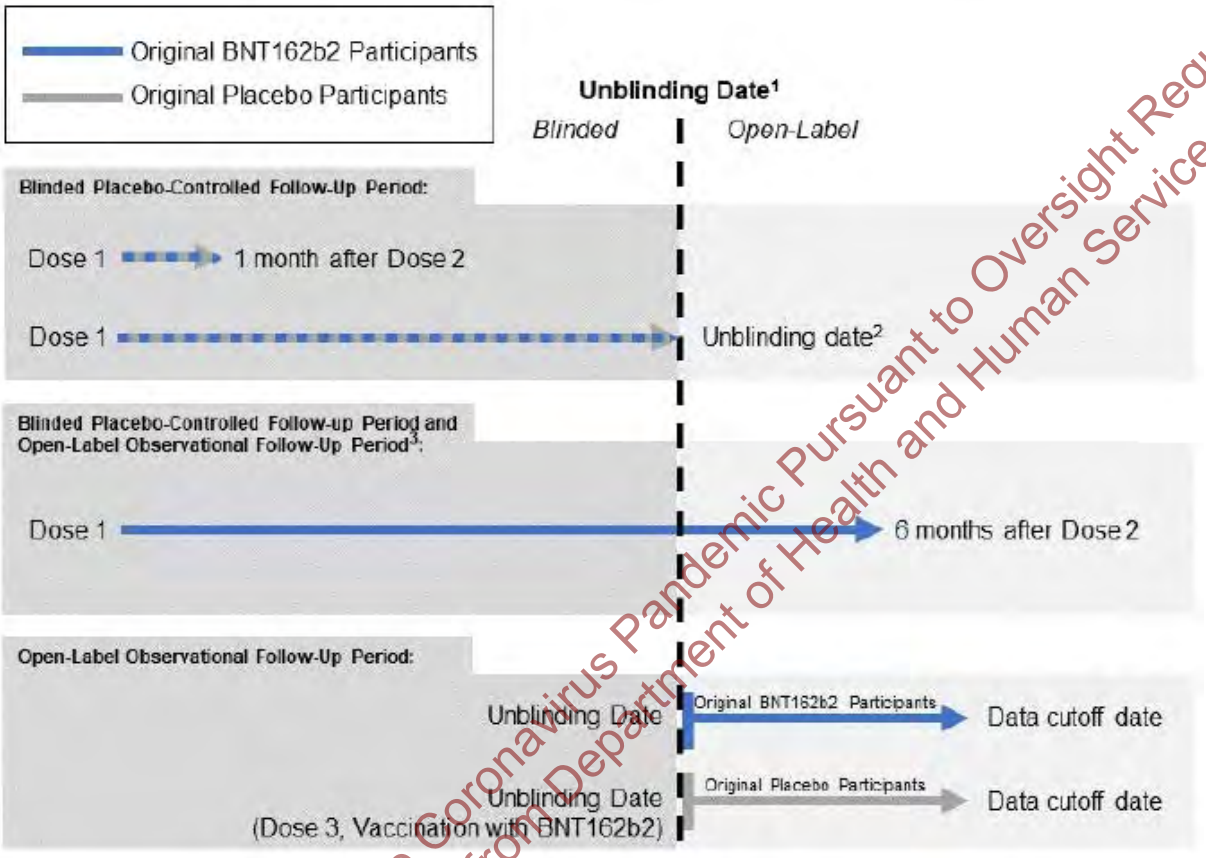
Safety data presented for Phase 3 of Study C4591001, based on the data cutoff date of March 13, 2021, include:

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)

Disposition	Vaccine Group (as Randomized) 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

Disposition	Vaccine Group (as Randomized) 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)	

Disposition	Vaccine Group (as Randomized) 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 , C4591001 , C4591001 and C4591001 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 partic pants 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)

Subgroup	Vaccine Group (as Randomized) 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

Subgroup	Vaccine Group (as Randomized) 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

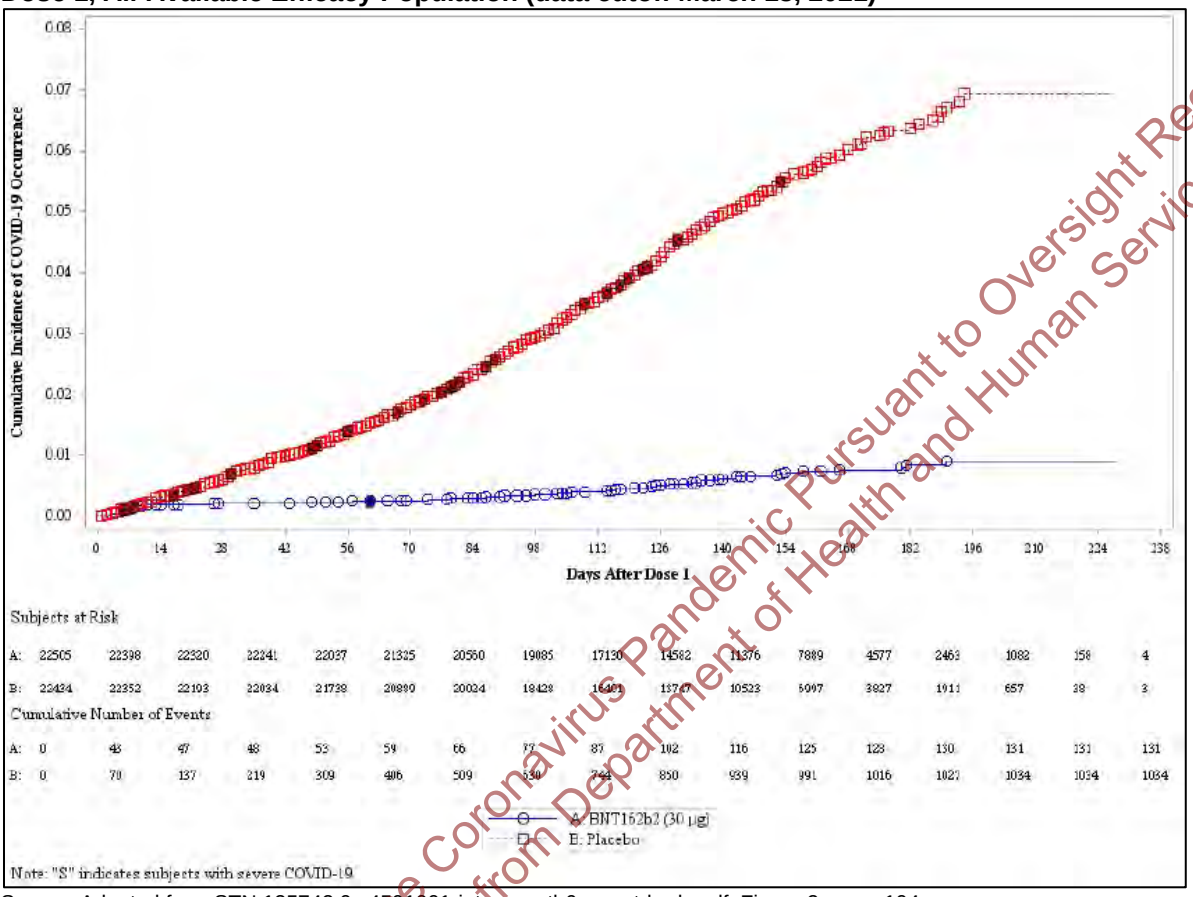
	Vaccine Group (as Randomized)		
Subgroup	**BNT162b2 (N[a] =19993) Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo (N[a] =20118) Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy (%) (95% CI[e])**
Overall	77 6.092 (19711)	833 5.857 (19741)	91.1 (88.8, 93.1)
Comorbidity			
No comorbidity	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 (713)	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°C	26 (1.3)	8 (0.4)	219 (11.8)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.1)	3 (0.2)	158 (8.5)	2 (0.1)
>38.4°C to 38.9°C	2 (0.1)	3 (0.2)	54 (2.9)	1 (0.1)
>38.9°C to 40.0°C	1 (0.0)	2 (0.1)	7 (0.4)	1 (0.1)
>40.0°C	0 (0.0)	0 (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.

<u>Open-label observational follow-up: from participant unblinding to the March 13, 2021 data cutoff</u>
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 demyelinatingpolyneuropathy, 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 (%)	**Placebo[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=% n[b]	Placebo (N[a] =100) n=% 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: 89.8;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

System Organ Class Preferred Term	16-55 Years of Age				>55 Years of Age				Total			
	BNT162b1 N=12995		Placebo N=13026		BNT162b1 N=8931		Placebo N=8895		BNT162b1 N=21926		Placebo N=21921	
	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 supraventricula	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 n (%)	 Placebo N=13026 n (%)	>55 Years of Age BNT162b1 N=8931 n (%)	 Placebo N=8895 n (%)	Total BNT162b1 N=21926 n (%)	 Placebo N=21921 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"

Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Epidemiology (OBE)
Division of Epidemiology (DE)

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

From:	Deborah L. Thompson, MD, MSPH Medical Officer, Analytic Epidemiology Branch (AEB) DE, OBE, CBER, FDA
To:	Ramachandra Naik, PhD Chair, Review Committee Office of Vaccines Research and Review (OVRR), CBER, FDA
Through:	Manette Niu, MD Branch Chief, AEB DE, OBE, CBER, FDA Narayan Nair, MD Division Director, DE OBE, CBER, FDA
Subject:	Review of Pharmacovigilance Plan
Sponsor:	Pfizer
Product:	BNT162b2 (COVID-19 Vaccine)
BLA Number:	125742/0
Proposed Indication:	Active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals ≥16 years of age.
Submission Date:	May 18, 2021
Action Due Date:	January 16, 2022

1 Objective and Scope

The purpose of this review is to assess the adequacy of the sponsor's proposed pharmacovigilance plan (PVP) submitted under the original BLA 125742/0 for post-marketing safety monitoring for BNT162b2 (COVID-19 vaccine) and to identify potential safety issues associated with the use of BNT162b2 that may need to be addressed through additional pharmacovigilance activities including safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) or a Risk Evaluation and Mitigation Strategy (REMS).

2 Product Information

2.1 Product Description

BNT162b2 contains a nucleoside-modified messenger RNA (modRNA) that encodes the viral spike (S) glycoprotein of SARS-CoV-2. Each vial of vaccine is diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose 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.

2.2 Authorized Indication and Dosing Regimen

The Pfizer-BioNTech COVID-19 Vaccine is currently authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals ≥12 years of age. The vaccine is administered intramuscularly as a series of two doses (0.3 mL each) given three weeks apart.

2.3 Proposed Product Indication and Dosing Regimen

The proposed indication for BNT162b2 is active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals ≥16 years of age. The vaccine is administered intramuscularly as a series of two doses (0.3 mL each) given three weeks apart.

3 Materials Reviewed

- Pharmacovigilance Plan, Version 1.0 (STN 125742/0.1, Module 1.16.1, dated May 17, 2021; received May 18, 2021)
- Pharmacovigilance Plan, Version 1.1 (STN 125742/0.20, sequence 0021, Module 1.16.1, dated July 28, 2021; received July 29, 2021)

- Cumulative Analysis of Post-authorization Adverse Event Reports (STN 125742/0, Module 5.3.6, received May 6, 2021)
- Summary of Clinical Safety (STN 125742/0, Module 2.7.4; received May 6, 2021)
- Draft Labeling Text (STN 125742/0.1, Module 1.14; received May 18, 2021)
- Post-authorization safety surveillance study protocols linked in the PVP
- Sponsor's IR responses
- VAERS database and data mining

4 Summary of Pertinent Regulatory History and Prior Marketed Experience

Pertinent regulatory history is shown in Table 1. BNT162b2 has received temporary authorization for emergency supply in 28 countries and conditional marketing authorization in 39 countries. As of August 4, 2021, over 194 million doses of BNT16b2 have been administered to over 88 million individuals in the U.S. under the EUA. Per the sponsor's Summary Monthly Safety Report (STN 19736.409), approximately [redacted] doses of BNT162b2 have been shipped worldwide from December 1, 2020 through June 30, 2021, which corresponds to approximately 757,863,718 estimated doses administered.

Table 1: Pertinent Regulatory History

Date	Regulatory Action
April 29, 2020	IND for BNT162b2 became effective
July 7, 2020	Fast Track Designation granted for individuals 18 years of age and older
December 11, 2020	Emergency Use Authorization (EUA 27034) granted for active immunization to prevent COVID-19 in individuals 16 years of age and older
May 10, 2021	FDA re-issued EUA letter to expand authorization for use in individuals 12 through 15 years of age with addition of following warning in Fact Sheet for Healthcare Providers: "Syncope (fainting) may occur in association with administration of injectable vaccines, in particular adolescents. Procedures should be in place to avoid injury from fainting."
May 18, 2021	Final roll of BLA 125742/0 submitted
June 25, 2021	EUA Fact Sheet revised to add Warnings for myocarditis and pericarditis following use of Pfizer-BioNTech COVID-19 Vaccine

5 Summary of Sponsor's Safety Database

5.1 Clinical Studies

There are two clinical studies for BNT162b2 which are summarized in Table 2.

Table 2: Summary of Clinical Studies for BNT162b2*

Study	Description	Number of subjects randomized	Data cut-off date
BNT162-01	Phase 1/2 first in human dose finding study, open-label, non-randomized, included two age cohorts: 18-55 years and 56-85 years; BNT162b2 was given at 5 dose levels (1, 3, 10, 20, 30 µg)	216	October 23, 2020
C4591001 (BNT162-02)	Phase 1/2/3 randomized, placebo-controlled, observer blind study for safety, immunogenicity, and efficacy		
	Phase 1: two age cohorts: 18-55 years and 65-85 years; 3 dose levels for BNT162b2: 10, 20, and 30 µg; randomized 4:1 to receive active vaccine or placebo; long term follow-up (LTFU) for AEs/SAEs for BNT162b2 30 µg group only	195 (30 in LTFU)	August 24, 2020 (March 13, 2021 for LTFU)
	Phase 2: two age cohorts: 18-55 years and 56-85 years; BNT162b2 30 µg dose; randomized 1:1 to receive active vaccine or placebo	360	September 2, 2020
	Phase 3: three age cohorts: 12-15, 16-55 years and >55 years; BNT162b2 30 µg dose; randomized 1:1 to receive active vaccine or placebo	43,847 (includes 360 subjects from Phase 2)	March 13, 2021

*Adapted from sponsor's Summary of Clinical Safety, Table 1.

Study BNT162-01

Study BNT162b2 is an ongoing, first-in-human, open-label, non-randomized Phase 1/2 dose finding and cohort expansion (for dose levels selected during dose finding) study conducted in Germany (not under U.S. IND) among healthy adults age 18 to 85 years of age. Four vaccine candidates from three different RNA platforms were tested. Key safety assessments included physical examinations, electrocardiograms, clinical laboratory tests, solicited local and systemic reactions (recorded in diaries for seven days post-dose), SARS-CoV-2 testing, adverse events (AEs), and serious adverse events (SAEs). Unsolicited treatment emergent AEs (TEAEs) were recorded for 28 days post-second dose. Adverse events of special interest (AESI) included enhanced respiratory disease or flu-like symptomatology that did not resolve after seven days.

Study C4591001

Study C4591001 (IND 019736) is a Phase 1/2/3 randomized, placebo-controlled, observer blind study for safety, immunogenicity, and efficacy. Participants are followed for 24 months. Participants ≥16 years who originally received placebo (i.e., normal saline) and became eligible for receipt of BNT162b2 were offered BNT162b2 in a phased process as part of the study.

Phase 1 evaluated two vaccine candidates (BNT162b1 and BNT162b2) and involved dose-level finding (three dose levels for BNT162b2: 10, 20, and 30 µg) among two age cohorts of healthy adults (18-55 and 65-85 years; n=195). Subjects were randomized 4:1 to receive active vaccine or placebo. Reactogenicity (i.e., local and systemic reactions) was assessed for up to seven days after each dose, AEs were assessed from dose 1 through 1 month after the last dose, and SAEs were assessed from dose 1 to six months after the last dose. Long-term follow-up for AEs and SAEs was conducted for the BNT162b2 30 µg cohort (n=30) from 1-month post-second dose to the unblinding date (approximately 6-months post-second dose).

Phase 2/3 was conducted to define the safety profile of BNT162b2 and involved administration of BNT162b2 (30 µg dose) to individuals in three age cohorts (12-15 years, 16-55 years and >55 years; n=43,847). Phase 2/3 participants were those judged by investigators to be at higher risk for acquiring COVID-19 (e.g., individuals who use mass transportation or frontline essential workers). Subjects were randomized 1:1 to receive active vaccine or placebo. Phase 2 was conducted to confirm the safety profile seen in Phase 1 and included the first 360 randomized subjects; reactogenicity was assessed for up to seven days after each dose and AEs/SAEs were assessed from dose 1 to 7-days post-second dose. Phase 3 assessed reactogenicity in a subset of subjects (n=9,839) for up to seven days after each dose. Adverse events and SAEs were assessed in all subjects for 1-month post-second dose and up to the unblinding

date. In addition, open-label AEs/SAEs were assessed among participants originally randomized to BNT162b2 (n=20,309) from the date of unblinding to the data cut-off (March 13, 2021). Open-label AEs/SAEs were assessed among participants who were originally randomized to placebo but were vaccinated with BNT162b2 after treatment disclosure (n=19,525) from the date of BNT162b2 vaccination to the data-cutoff (March 13, 2021). No AEs of special interest were defined for Study C4591001.

5.2 Adverse Events

In Study BNT162-01 most solicited local and systemic reactions were mild or moderate in severity and were short-lived after dosing. Most unsolicited AEs were also mild to moderate in severity and all resolved; there were no unanticipated safety findings. There were no AESIs, deaths, or treated-related SAEs reported among participants who received BNT162b2 in Study BNT162-01. Similarly, in Phase 1 and 2 of Study C4591001, reactogenicity was mostly mild to moderate and short-lived after dosing; the AE profile did not suggest any serious safety concerns. There were no treatment-related SAEs or deaths.

In Phase 3 of Study C4591001, solicited local reactions occurred more commonly in the BNT162b2 group as compared with the placebo group; the majority of local reactions were mild or moderate in severity after both first and second doses and in both younger (≤55 years) and older age groups (>55 years). Solicited systemic events and use of antipyretic/pain medication were generally reported less frequently in the placebo group as compared with the BNT162b2 group for both age groups and doses, with the exception of vomiting and diarrhea which were reported at similar frequencies between BNT162b2 and placebo groups. The majority of solicited systemic events were mild or moderate in severity. Solicited systemic events occurred more frequently after Dose 2 of BNT162b2 as compared with Dose 1 in both younger and older age groups. Reactogenicity AEs were generally milder and less frequent in the older age group as compared with the younger age group.

In the blinded placebo-controlled follow-up period (n=43,847), 30.2% of BNT162b2 recipients and 13.9% of placebo recipients had any AE from Dose 1 to 1-month after Dose 2 and 0.6% and 0.5%, respectively, had an SAE; there were three deaths in the BNT162b2 group and five deaths in the placebo group. The most frequently reported AEs were reactogenicity events including injection site pain (13.3% BNT162b2 group vs 1.8% placebo group), pyrexia (6.9% vs 0.4%), fatigue (6.7% vs 1.7%), chills (6.2% vs 0.5%), headache (6.1% vs 1.9%), myalgia (5.7% vs 0.8%), pain (2.9% vs 0.3%), and arthralgia (1.2% vs 0.5%). Among those in the BNT162b2 group, the overall AE frequencies were higher in the younger age group (32.6%) as compared with the older age group (26.7%).

From Dose 1 to the unblinding date, the AEs with the highest incidence rates were consistent with the AEs in the Dose 1 to 1-month after Dose 2 analysis. There were also similar incidence rates of SAEs (3.2 per 100 person-years for BNT162b2 group vs 3.3 per 100 person-years for placebo group) and deaths among BNT162b2 and placebo

recipients (0.2 per 100 person-years for both groups; 15 vs 14 deaths, respectively). There were four related-SAEs in the BNT162b2 group (one each of lymphadenopathy, shoulder injury related to vaccine administration, ventricular arrhythmia, and paresthesia of right leg) and one related-SAE in the placebo group (psoriatic arthropathy). The 15 deaths in BNT162b2 group were due to: cardiac arrest (n=4), arteriosclerosis (n=2), and one each of COVID-19 pneumonia, cardiac failure congestive, cardiorespiratory arrest, chronic obstructive pulmonary disease (COPD), emphysematous cholecystitis, hypertensive heart disease, metastatic lung cancer, sepsis, septic shock, shigella sepsis, and an unevaluable event; multiple contributing causes of death could be reported for each subject. The 14 deaths in the placebo group were due to COVID-19 (n=2), multiple organ dysfunction syndrome (n=2), myocardial infarction (n=2), pneumonia (n=2), lacking specific cause (n=2; one "death" and one "missing") and one each of acute respiratory failure, aortic rupture, metastatic biliary cancer, cardiac arrest, cardiorespiratory arrest, dementia, hemorrhagic stroke, liver metastases, and overdose. None of the deaths during the Dose 1 to unblinding date time period were assessed by investigators as related to the study intervention.

From the unblinding date to the data cut-off, the incidence rates of AEs were markedly reduced relative to the AEs reported from Dose 1 to the unblinding date among the original BNT162b2 recipients (n=21,926) (8.8/100,000 person-years vs 83.2/100,000 person-years, respectively). There were 55 SAEs during this time period among the original BNT162b2 recipients, including one related-SAE of myocardial infarction (participant in younger age group with no past medical history [PMH], onset 71-days after Dose 2, resolved same day). There were three deaths among the original BNT162b2 participants (all in the older age group; one each due to road traffic accident, lung metastases, and myocardial infarction); none of the deaths were assessed by investigators as related to study intervention.

Among the 19,525 participants who originally received placebo and then received BNT162b2 after unblinding, the most frequently reported AEs overall were related to reactogenicity and were consistent with AEs reported among the group that was originally randomized to receive BNT162b2. After vaccination with BNT162b2, there was one related-SAE of anaphylactoid reaction in a patient with an ongoing medical history of drug hypersensitivity and food and seasonal allergies (onset 2-days post-1st dose of BNT162b2; treated with self-administered epinephrine pen and resolved same day). Two deaths occurred following vaccination with BNT162b2 (both in the older age group; one each due to cardiorespiratory arrest and completed suicide), neither of which were assessed by investigators as related to the study intervention.

The sponsor also provided a review of AEs of interest requested by FDA (hypersensitivity/anaphylaxis, Bell's palsy/facial paralysis, lymphadenopathy, and appendicitis) and the Center for Disease Control and Prevention's (CDC) AESI list for COVID-19 vaccines. This review was focused on the Dose 1 to unblinding time period. For hypersensitivity, there was a higher number and percentage of participants in the BNT162b2 vs placebo groups (182 [0.83%] vs 161 [0.73%], respectively), which was mainly due to skin and subcutaneous tissue disorders (134 [0.61%] vs 119 [0.54%]),

including rash (62 [0.28%] vs 52 (0.24%]), urticaria (18 [0.08%] vs 15 [0.07%]), rash pruritic (8 [0.04%] vs 6 [0.03%]), rash maculo-papular (7 [0.03%] vs 4 [0.02%]), and eczema (7 [0.03%] vs 3 [0.01%]). There were three hypersensitivity SAEs during the blinded placebo-controlled follow-up period: two in the BNT162b2 group (anaphylactic reaction following bee sting and drug hypersensitivity to an antibiotic) and one in the placebo group (anaphylactic shock due to an ant bite); none were considered by investigators as related to the study intervention. Among the original placebo group participants who then received BNT162b2 after unblinding there was one anaphylactoid reaction (assessed as related; reviewed in section 5.2 of this memorandum). For Bell's palsy, there were four cases in the BNT162b2 group (two of which were considered related by investigators) and two in the placebo group during the blinded placebo-controlled follow-up period. Among those who originally received placebo and then received BNT162b2 after unblinding, there were three participants who experienced facial paralysis (all considered related by investigators). Lymphadenopathy was reported in 87 (1.0 per 100 person-years [PY]) participants in the BNT162b2 group compared to 8 (0.2 per 100 PY) participants in the placebo group. One lymphadenopathy event (right axilla, normal lymph node biopsy) was considered a related-SAE in the BNT162b2 group and resolved within 66 days. Appendicitis was reported for a total of 15 BNT162b2 participants, including one case of perforated appendicitis, as compared with 12 total reports of appendicitis in the placebo group, including two cases of complicated appendicitis, and one case of perforated appendicitis. All appendicitis cases were reported as SAEs and none were considered related to study intervention by investigators. Among CDC-defined AESIs that occurred from Dose 1 to unblinding in the Phase 2/3 study, the overall number and percentage of participants with any unsolicited AESIs within selected SMQs were similar between the BNT162b2 (224 [1.02%]) and placebo groups (217 [0.99%]); most individual AESI categories were similar between BNT162b2 and placebo groups (or higher in the placebo group) with the exception of hypersensitivity which is discussed above.

Reviewer comment: The sponsor submitted a revised PVP (Version 1.1) on July 29, 2021 which added the important identified risks of myocarditis and pericarditis and also included clinical trial data for myocarditis and pericarditis through June 18, 2021. The revised PVP indicated that among participants age 16 years and older two SAE cases of pericarditis were found from Phase 3 clinical trial C4591001; both SAEs were deemed by study investigators as not related to study treatment. There were no clinical trial reports of myocarditis as an SAE. Review of the sponsor's safety data did not identify new safety concerns that required further amending the sponsor's PVP.

5.3 Sponsor's Cumulative Analysis of Post-Authorization Adverse Event Reports

Cumulative post-authorization safety data, through February 28, 2021:

The sponsor provided a summary of cumulative post-authorization safety data, including U.S. and foreign post-authorization adverse event reports received through February 28, 2021. The safety database includes AEs reported spontaneously, by health authorities, and from published medical literature, Pfizer-sponsored marketing

programs, non-interventional studies, and serious AEs reported from clinical studies regardless of causality assessment.

There was a total of 42,086 AE reports containing 158,893 events. Most reports were from the U.S. (13,739), followed by the United Kingdom (13,404), Italy (2,578), Germany (1,973), France (1,506), Portugal (866), and Spain (756); the remaining 7,324 reports were from 56 other countries. Most reports were in females (29,914 (71.1%) reports); there were 9,182 (21.8%) reports for males and 2,990 (7.1%) with no sex data. Reports by age groups were as follows: ≤17 years (n=175), 18-30 years (n=4,953), 31-50 years (n=13,886), 51-64 years (n=7,884), 65-74 years (n=3,098), ≥75 years (n=5,214), and unknown (n=6,876). The most commonly reported MedDRA Preferred Terms (PTs) occurring ≥10% were headache (24.1%), pyrexia (18.2%), fatigue (17.4%), chills (13.1%), vaccination site pain (12.3%), nausea (12.3%), and myalgia (11.7%).

The sponsor included a summary of post-authorization AE reports for each safety concern listed in the PVP (see Section 7 of this memorandum for PVP summary). For anaphylaxis (important identified risk), there were 1,002 cases that met the Brighton Collaboration (BC) definition level 1 (highest level of certainty) through 4 (reported event with insufficient evidence to meet case definition), including nine fatal events. The sponsor concluded that evaluation of these cases did not reveal any significant new safety information and that anaphylaxis and non-anaphylactic hypersensitivity reactions are appropriately described in the product labeling (Sections 4 Contraindications, 5.1 Management of Acute Allergic Reactions, and 6 Adverse Reactions of the proposed USPI). In addition, the sponsor did not identify any cases definitively considered to be vaccine-associated enhanced disease (VAED) or vaccine-associated enhanced respiratory disease (VAERD) and concluded that VAED/VAERD remains a theoretical risk for the vaccine (i.e., important potential risk).

Among “missing information” categories in the PVP, there were 413 reports (84 serious and 329 non-serious) involving use in pregnancy and lactation. There were 270 maternal cases and four fetus/infant cases. Pregnancy outcomes were reported for 32 cases (including twins who each had two different outcomes reported) and included spontaneous abortion (n=23); outcome pending (n=5); premature birth with neonatal death, spontaneous abortion with intrauterine death (2 each); spontaneous abortion with neonatal death and normal outcome (1 each). Among mothers, 124 cases (75 serious and 49 non-serious) were pregnancy-related PTs: spontaneous abortion (n=25); uterine contraction during pregnancy, premature rupture of membranes, abortion, abortion missed, and fetal death (1 each). The four fetus/infant cases reported the following PTs: exposure during pregnancy, fetal growth restriction, maternal exposure during pregnancy, premature baby (2 each); and death neonatal (n=1). There were 133 reports in breastfed infants, including 17 cases (3 serious and 14 non-serious) that reported clinical events that occurred in an infant/child exposed to vaccine via breastfeeding: pyrexia (n=5); rash (n=4); infant irritability (n=3); infantile vomiting, diarrhea, insomnia, and illness (2 each); poor feeding infant, lethargy, abdominal discomfort, vomiting, allergy to vaccine, increased appetite, anxiety, crying, poor quality sleep, eructation, agitation, pain, and urticaria (1 each).

There were 34 reports (24 serious and 10 non-serious) involving 132 AEs indicating use in pediatric individuals <12 years of age. Events reported more than once included product administered to patient of inappropriate age (n=27); off label use (n=11); pyrexia (n=6); product use issue (n=5); fatigue, headache, nausea (4 each); vaccination site pain (n=3); upper abdominal pain, COVID-19, facial paralysis, lymphadenopathy, malaise, pruritis, and swelling (2 each).

There were 1,665 reports concerning vaccine effectiveness (1,649 drug ineffective and 16 vaccination failure). Among the 16 cases of vaccination failure, eight individuals had onset of COVID-19 symptoms within 7-13 days post-2nd vaccine dose and six individuals had onset within 15-29 days post-2nd dose. Six reports were asymptomatic COVID-19 infections. For each concern listed in the PVP, the sponsor concluded that no new safety signals were identified in post-authorization AE data.

The sponsor also evaluated AEs in the following AESI categories: anaphylactic reactions, cardiovascular, COVID-19, dermatological, hematological, hepatic, facial paralysis, immune-mediated/autoimmune, musculoskeletal, neurological (including demyelination), other (e.g., herpes viral infections) pregnancy-related, renal, respiratory, thromboembolic events, stroke, and vasculitic events, and concluded that the cumulative case review did not raise new safety issues.

Finally, the sponsor provided information on reports potentially indicative of medication errors. There were 2,056 reports of medication errors, with or without associated AEs. Of these, there were seven death reports, and 1,569 (76.3%) reports were medically confirmed. The sponsor indicated that all medication errors reported in death reports were assessed as non-serious events with unknown outcomes and concluded that based on available information, including causes of death, the relationship between the medication error and the death is weak. Overall, most reports (n=1,371, 66.7%) included only medication errors without any associated clinical adverse events (e.g., poor quality product administered, product temperature excursion issue, underdose, circumstance or information capable of leading to medication error). In 685 reports, there were AEs co-reported; the most frequent AEs were headache (n=187), pyrexia (n=161), fatigue (n=135), chills (n=127), pain (n=107), vaccination site pain (n=100), nausea (n=89), myalgia (n=88), pain in extremity (n=85), arthralgia (n=68), off label use (n=57), dizziness (n=52), lymphadenopathy (n=47), asthenia (n=46), and malaise (n=41).

Reviewer comment: The sponsor's cumulative summary of post-authorization data as of the data lock point, February 28, 2021, showed that the most frequently reported AEs were consistent with AEs described in the EUA Fact Sheet (i.e., headache, pyrexia, fatigue, chills, vaccination site pain, nausea, and myalgia).

Post-authorization safety data, updated through June/July 2021:

The sponsor submitted a revised PVP (Version 1.1) on July 29, 2021 which included post-authorization data for myocarditis and pericarditis among individuals 16 years of age and older through June 18, 2021. There was a total of 823 AE reports, including 490 reports of myocarditis and 372 reports of pericarditis; 38 reports included both myocarditis and pericarditis. Among the 490 myocarditis reports, 464 (including 78 U.S reports) met Brighton Collaboration Level 1 to 4 (Version 1.4.2; May 30, 2021). The majority of myocarditis reports (n=325, 66.3%) were in males and the median age was 32 years (range=16-97 years); there were 14 death reports. Among the 371 reports of pericarditis (including 68 U.S. reports), 181 (48.8%) were in males and 185 (49.9%) occurred in females (five reports did not include sex); the median age was 51 years (range=16-92 years) and there were three death reports.

The sponsor also provided post-authorization data through June 18, 2021 for myocarditis and pericarditis in individuals age 12-15 years. There were 13 reports of myocarditis (none were deaths); 11 met Brighton Collaboration Level 4 (i.e., reported event with insufficient evidence to meet the case definition) and two met Brighton Collaboration Level 5 (i.e., not a case); 10 (90.9%) were male and 1 (9.1%) was female; the median age was 14 years (range=12-15 years). There were four reports of pericarditis (none were deaths); all were male, and the median age was 13.5 years (range=12-15 years).

The sponsor indicates that a mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established, however myocarditis and pericarditis are considered an important identified risk in the PVP. The sponsor concluded that the vaccine continues to have a favorable risk benefit balance and that considering the low rates of myocarditis and pericarditis reported following vaccination, balanced with the risk of death and illness (including myocarditis) from SARS-CoV-2, the public health impact of post-vaccination myocarditis and pericarditis is minimal.

Reviewer comment: There are ongoing analyses, by the sponsor and FDA, to further characterize the new safety signal for myocarditis and pericarditis after the Pfizer-BioNTech COVID-19 vaccine. As described above, the majority of myocarditis reports occurred in males, under 30 years of age. Please see section 6.1 and 8.2 for additional discussion.

6 Summary of FDA Post-Authorization Safety Data

6.1 Vaccine Adverse Event Reporting System Data

Since its authorization on December 11, 2021 through June 11, 2021 a total of 151,543 reports, including 24,961 serious reports (3,512 of which were death reports), have been received and processed (coded, redacted, and quality assurance performed) by the Vaccine Adverse Event Reporting System (VAERS) for the Pfizer-BioNTech COVID-19 vaccine. Among all reports the top 10 most frequently reported PTs are headache, fatigue, pyrexia, chills, pain, dizziness, nausea, pain in extremity, arthralgia,

and injection site pain. Among serious reports the top 10 most frequently reported PTs are SARS-CoV-2 test, COVID-19, dyspnea, headache, fatigue, pyrexia, death, SARS-CoV-2 test positive, dizziness, and nausea.

Reviewer comment: Most of the commonly reported PTs in VAERS reports are labeled events in the EUA Fact Sheet (i.e., headache, fatigue, fever, chills, pain, joint pain, nausea, vomiting) or a non-specific AE that could be a possible vaccine stress-related response (i.e., dizziness). The PTs of SARS-CoV-2 test and SARS-CoV-2 test positive refer to testing for SARS-CoV-2 infection. The PT of "dyspnea" is a non-specific symptom that may be present in a variety of conditions both serious and non-serious. Dyspnea associated with FDA/CDC AESIs, such as acute myocardial infarction, pulmonary embolus, or myopericarditis, is monitored as part of routine surveillance for AESIs and/or through death reviews.

VAERS was queried for the safety concerns listed in the PVP (Section 7 of this memorandum).

Anaphylaxis:

For the important identified risk of anaphylaxis, VAERS was queried from December 11, 2020 (the date of authorization) to June 11, 2021. The query was run on June 17, 2021 using the PTs anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, or anaphylactoid shock. The search returned 1,034 reports (1,009 U.S. reports), including 524 serious reports; 12 of the serious reports were death reports. There were 167,680,391 doses of the Pfizer-BioNTech Covid-19 vaccine administered in the U.S. as of June 14, 2021. This equates to a crude reporting rate for anaphylaxis of 6.0 cases per million doses. Among the 12 deaths, five individuals were female, six were male, and one was of unknown sex; the median age was 81 years (range= 58-86 years; 3 individuals were of unknown age) and the median onset as calculated by VAERS dates was zero days post-vaccination (range=0-16 days). Nine individuals who died reported various chronic underlying conditions including hypertension, asthma, diabetes mellitus, ischemic cardiomyopathy, myocardial infarction, atrial fibrillation, arrythmia, obesity, sleep apnea, and dementia. Three individuals who died had a history of hypersensitivity to penicillin, contrast imaging, or food/fruit allergy. One individual had a history of COVID-19 one-month prior to vaccination and one individual was diagnosed with concomitant COVID-19 pneumonia and acute hypoxic respiratory failure post-vaccination.

Reviewer comment: Allergic reactions and anaphylaxis are labeled in the EUA Fact Sheet for this product. In addition, the EUA Fact Sheet cites CDC clinical guidelines which recommend observation periods following COVID-19 vaccination. Review of VAERS reports did not identify new safety concerns related to anaphylaxis. Limitations to interpreting this information include that VAERS data are based on passive surveillance and important limitations of passive surveillance data include missing/inaccurate data, unconfirmed diagnoses, potential under-reporting, and variable or incomplete reporting. The methodology for calculating crude reporting rates was

based on reports retrieved from automated queries, which may include duplicate cases as not all cases were manually reviewed to apply the Brighton Collaboration case definition criteria for anaphylaxis (Ruggeberg, 2007). (Note that this is a key difference in the above methodology compared to previous publications [MMWR Jan 15, 2021; Gee, 2021; Shimabukuro, 2021], which calculated reporting rates based only on adjudicated cases that were confirmed through medical record review or direct contact with the provider.) The incidence of anaphylaxis after receipt of the Pfizer-BioNTech COVID-19 vaccine is comparable with those reported after receipt of other vaccines (Gee, 2021).

Myocarditis and pericarditis:

After the issuance of the EUA, FDA and CDC received reports of myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine. In accordance with FDA recommendations, the sponsor added myocarditis and pericarditis as important identified risks in the PVP. A VAERS search was performed for the timeframe from December 11, 2020 (the date of authorization) to June 21, 2021. The query was run on June 23, 2021 utilizing the PTs autoimmune myocarditis, autoimmune pericarditis, eosinophilic myocarditis, hypersensitivity myocarditis, myocarditis, pericarditis, pericarditis adhesive, pericarditis constrictive, and pleuropericarditis.

The query returned 1,023 reports (1012 U.S. reports), including 809 serious reports (seven were death reports concerning six unique individuals), of which 652 reports were in individuals under 30 years of age. The reports concerned 775 (75.8%) males and 238 (23.3%) females; 10 reports concerned individuals of unknown sex. The median age was 21 years (range=12-86 years). The median onset post-vaccination as calculated by VAERS dates was 3 days (range=0-151 days). The six unique death reports (3 U.S. and 3 foreign reports) concerned three males and three females; the median age at death was 66 years (range=19-81 years) and the median onset post-vaccination was 4 days (range=1-22 days). Four deaths occurred following the second dose, one following the first dose, and for one the dose number was not reported. Most death reports contained limited information or described concurrent medical conditions and/or risk factors that might have contributed to the death. A summary of each death report is listed below:

1394140: 78-year male with no reported PMH died [redacted] post-2nd vaccine. An autopsy revealed myocarditis, but limited details were provided.

1044420: 36-year male with history of anosmia and influenza-like illness (ILI) developed non-specific ILI symptoms a few days post-vaccination. Twenty-two days post-2nd vaccination he developed low grade fevers, malaise, and sore throat. Testing revealed a negative SARS-CoV-2 test and a positive coronavirus nucleocapsid IgG. His symptoms progressed and the patient ultimately deteriorated and died. Autopsy findings included: heart with multifocal myocarditis with mixed inflammatory infiltrate, myocyte necrosis, microthrombi. The death certificate listed the following causes of death: hemorrhagic shock, d/t intraperitoneal bleed, d/t coagulopathy, d/t post COVID-19 syndrome.

1340821: 60-year female reported to have endocarditis following first dose and then myocarditis post-2nd dose (reported by friend, limited details).

1070309: Foreign report: 72-year female with PMH of cardiac arrest, chest pain, high cholesterol, neoplasm, acute myeloid leukemia, hypertension, high BMI, and GERD had chest pain and pericarditis 3-days post-1st dose. She suffered a cardiac arrest 7-days post-vaccination and died [redacted] days post-vaccination due to pericarditis.

1048413: Foreign report: 19-year male with no PMH experienced accelerated heartbeat, shortness of breath (SOB), and sharp pains radiating down left arm 5-days post-2nd vaccination. He was hospitalized in intensive care unit (ICU) and died. The reported cause of death was myocarditis.

1048221: Foreign report: 81-year female with history of COVID-19 experienced septic shock, extensive myo- and pericarditis, and multiple organ failure 3-days post-vaccination, died [redacted] days post-vaccination; autopsy-determined cause of death: Carditis pericardium myocardium.

In addition to review of reports from automated queries, all U.S. death reports are manually reviewed, and the following death was identified:

1406840: 13-year male with attention deficit hyperactivity disorder and developmental coordination disorder experienced flu-like symptoms for [redacted] days and then was found deceased; onset of symptoms 1-day post-vaccination. The preliminary autopsy report revealed cardiomegaly with biventricular dilatation, bilateral serous pulmonary effusions and serous pericardial effusion, marked pulmonary edema and congestion, and moderate degree of diffuse cerebral edema; SARS-CoV-2 and influenza A/B tests, toxicology, and determination of the cause of death are pending.

Furthermore, observed to expected (O/E) analyses were performed for risk windows of 7 days and 21 days, stratified by age, sex and dose, using U.S. data retrieved from automated queries of the VAERS database (data lock point July 6, 2021). The following PTs were used: atypical mycobacterium, pericarditis, autoimmune myocarditis, autoimmune pericarditis, bacterial pericarditis, coxsackie myocarditis, coxsackie pericarditis, cytomegalovirus myocarditis, cytomegalovirus pericarditis, enterovirus myocarditis, eosinophilic myocarditis, hypersensitivity myocarditis, immune-mediated myocarditis, myocarditis, myocarditis bacterial, myocarditis helminthic, myocarditis infectious, myocarditis meningococcal, myocarditis mycotic, myocarditis post infection, myocarditis septic, pericarditis, pericarditis adhesive, pericarditis constrictive, pericarditis helminthic, pericarditis infective, pericarditis mycoplasmal, pleuropericarditis, purulent pericarditis, viral myocarditis, and viral pericarditis. The vaccine administration data lock point for the O/E analysis was June 30, 2021. Only results for 7-day risk windows are shown in Tables 3 and 4 (relative risks [RR] with 95% CI >1 in **bold** font). The O/E analysis, stratified by age and dose number, indicates that the observed number of cases exceeds the expected number of cases (based on pre-COVID-19 pandemic U.S. population-based background incidence rates). The reporting rate and RR was higher among males than females for

almost all age groups and higher following dose 2 as compared to dose 1 in most age groups for both males and females. This trend was higher in the 7-day risk window compared to the 21-day risk window, and in the younger age groups. Important limitations of passive surveillance data include missing/inaccurate data, unconfirmed diagnosis and potential under-reporting. There is ongoing follow-up of the reports to obtain additional medical records for assessment of cases.

Table 3: Reporting Rates and Relative Risk (RR) of Myocarditis and Pericarditis Post Vaccination in Males using a 7-Day Risk Window

Age Group (years)	Background Rate*	Dose 1 Reporting Rate**	Dose 1 RR[ł] (95% CI)	Dose 2 Reporting Rate**	Dose 2 RR[ł] (95% CI)
12 - 17	2.16 [a]	0.99	**23.94 (17.02-32.73)**	10.22	**246.84 (219.83-276.26)**
18 - 24	2.16	0.48	**11.5 (6.7-18.42)**	5.91	**142.84 (122.17-166)**
25 - 29	2.16	0.26	**6.2 (2.49-12.78)**	1.55	**37.44 (26.08 - 52.06)**
30 - 39	6.1[b]	0.17	1.45 (0.7 -2.67)	0.88	**7.56 (5.49-10.14)**
40 - 49	6.1	0.12	1.04 (0.42-2.13)	0.53	**4.49 (2.93-6.58)**
50 - 64	6.1	0.07	0.59 (0.24-1.22)	0.14	1.16 (0.6-2.03)
≥65	6.1	0.07	0.63 (0.25-1.3)	0.07	0.61 (0.22-1.33)

*Background rates are rates per 100,000 persons per year.
**Reporting rates are per 100,000 doses of vaccine
[ł]Relative Risk (RR) is the reporting rate compared to the background rate when applied to the proportion of individuals vaccinated in each age group to July 1, 2021
[a]Gubernot et al, U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines
[b]Roth et al, Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019

Table 4: Reporting Rates and Relative Risk of Myocarditis and Pericarditis post Vaccination in Females using a 7-Day Risk Window

Age Group (years)	Background Rate*	Dose 1 Reporting Rate**	Dose 1 RR[ł] (95% CI)	Dose 2 Reporting Rate**	Dose 2 RR[ł] (95% CI)
12 - 17	2.16[a]	0.15	**3.51 (1.29-7.64)**	1.06	**25.49 (17.55-35.8)**
18 - 24	2.16	0.1	2.32 (0.63-5.94)	0.58	**14.13 (8.63 - 21.82)**
25 - 29	2.16	0.07	1.59 (0.19-5.75)	0.2	**4.74 (1.54 - 11.05)**
30 - 39	4.4[b]	0.18	**2.16 (1.12-3.78)**	0.16	1.91 (0.87 - 3.63)
40 - 49	4.4	0.06	0.72 (0.19-1.83)	0.32	**3.74 (2.22 - 5.92)**
50 - 64	4.4	0.1	1.23 (0.64-2.16)	0.19	**2.23 (1.34-3.48)**
≥65	4.4	0.04	0.5 (0.16-1.17)	0.08	0.91 (0.39-1.79)

*Background rates are rates per 100,000 persons per year.
**Reporting rates are per 100,000 doses of vaccine
[ł]Relative Risk (RR) is the reporting rate compared to the background rate when applied to the proportion of individuals vaccinated in each age group to July 1, 2021
[a]Gubernot et al, U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines
[b]Roth et al, Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019

Reviewer comment: *Myocarditis and pericarditis emerged as a safety signal in VAERS and was jointly reviewed by FDA and CDC. Please see section 8.2 for further discussion of this safety signal.*

Vaccine-associated enhanced disease (VAED):

There are not specific PTs for the important potential risk of vaccine-associated enhanced disease (VAED). Please see reviewer comments below regarding the VAERS search for PTs related to vaccine effectiveness.

Other:

Categories in the PVP that are considered “missing information” (i.e., use during pregnancy and lactation, vaccine effectiveness, and use in pediatric individuals <12 years of age), were also queried in VAERS. A VAERS search from December 11, 2020 (the date of authorization) to June 11, 2021 (run on June 22, 2021) for the System Organ Class (SOC) Pregnancy, Puerperium and Perinatal Conditions returned 1,050 reports, including 175 serious reports, 11 of which were deaths. Among the 11 death reports, eight involved a fetal (n=5) or infant death (n=3) and three were maternal deaths. The five fetal deaths were either miscarriage or intrauterine death that occurred less than two weeks post-maternal vaccination. The three infant deaths were: one death from thrombotic thrombocytopenic purpura (TTP) in a breastfed infant (symptom onset 1-day post-2nd-maternal vaccination), one report of premature birth 6 days post-vaccination with subsequent death (vaccine exposure during second trimester), and one report of premature birth at 21 weeks gestation with subsequent death 2-hours after birth (birth 13-days post-maternal vaccination and complicated by meconium aspiration and maternal chorioamnionitis due to a *Staphylococcus aureus* infection). The three maternal deaths were: a 32-year old female with asymptomatic Factor V Leiden who died 4-days after childbirth and 52-days post-vaccination (limited details); a 42-year old female with no reported PMH who died of a massive pulmonary embolus at 27-weeks gestation, and a 38-year old female with Type 1 diabetes mellitus, hemochromatosis, and sleep apnea who experienced maternal cardiac arrest with likely amniotic fluid embolism and disseminated intravascular coagulation (DIC) 14-days post-vaccination.

A separate query (run on July 13, 2021) of VAERS PT event counts for the SOC Pregnancy, Puerperium and Perinatal Conditions (from December 11, 2021 to June 11, 2021) showed a total of 1,589 PTs, including 546 PTs reported for serious reports and 21 PTs reported for deaths. Among serious reports, the top 10 most frequently reported PTs in the SOC Pregnancy, Puerperium and Perinatal Conditions were: exposure during pregnancy (n=189), abortion spontaneous (n=83), maternal exposure during pregnancy (n=40), fetal death (n=27), premature delivery (n=20), premature labor (n=17), delivery (n=15), induced labor (n=14), premature baby (n=11), and premature separation of placenta (n=9). Among death reports, PTs in the SOC Pregnancy, Puerperium and Perinatal Conditions reported more than once included exposure during pregnancy (n=4), maternal exposure during pregnancy (n=4), fetal death (n=4), spontaneous abortion (n=2), and premature baby (n=2).

Reviewer comment: Vaccine safety in pregnant women is being evaluated in a randomized controlled trial conducted by the sponsor, active surveillance studies conducted by the sponsor, and the CDC v-safe program. The background incidence of miscarriage varies by age and ranges from 10% in women aged 25-29 years up to 53% in women aged 45 years and older (Magnus, 2019). Review of the most common PTs reported in the SOC Pregnancy, Puerperium and Perinatal Conditions and individual review of VAERS death reports did not suggest patterns indicating a new safety concern that needs to be addressed in the PVP.

For “missing information” regarding vaccine effectiveness, VAERS was searched for the timeframe December 11, 2020 to June 11, 2021 (query run on June 17, 2021) using PTs for vaccination failure and drug ineffective. The search returned 1,788 reports that included the PT “vaccination failure” (n=254) and/or “drug ineffective” (n=1,565); 31 reports contained both PTs. Among the 254 reports including the PT vaccination failure, there were 24 serious reports and eight deaths. Among the eight deaths (three U.S. and five foreign reports), six were female and two were male; the median age was 71 years (range=37-98 years) and median onset as calculated by VAERS dates was 10 days post-vaccination (range=7-63 days). Most deaths occurred in individuals with reported underlying co-morbidities. Among the 1,565 reports of drug ineffective, there were 258 serious reports including 120 deaths. Among the 120 deaths, the majority (n=103, 86%) were foreign reports; 41 individuals were female, 57 were male, and 22 were of unknown sex; the median age was 84 years (range=17-99 years; 29 [24%] with unknown age) and median onset as calculated by VAERS dates was 4 days post-vaccination (range=0-26 days; 22 [18%] had incalculable VAERS dates). Most deaths occurred in individuals with reported underlying co-morbidities or unknown medical history.

Reviewer comment: There are VAERS reports of deaths due to COVID-19 in patients reported to be fully vaccinated. It is expected there may be some cases of vaccination failure, especially in elderly or immunocompromised subjects. Infection with a variant SARS-CoV-2 virus for which vaccination is less effective is also a possibility. Many reports concern elderly individuals with co-morbidities or contain limited details which makes complete assessment difficult. Generally, passive surveillance and spontaneous adverse event reporting cannot be used to draw conclusions regarding vaccine effectiveness due to the lack of a control group, reporter bias, and underreporting. Severe manifestations and death from COVID-19 raise the possibility of vaccine-associated enhanced disease (VAED), which has overlapping clinical manifestations with natural SARS-CoV-2 infection, making it difficult to differentiate VAED from severe COVID-19 disease in individual VAERS reports (Munoz, 2021). VAED is being assessed in a continuation of the Phase 3 clinical studies and active surveillance studies being conducted by the sponsor.

For “missing information” regarding individuals <12 years of age, VAERS was searched for the timeframe December 11, 2020 to June 11, 2021 (query run on June 22, 2021). There was a total of 273 reports in children <12 years of age, including 31 serious reports and two death reports. Among the 31 serious reports, the most commonly reported PTs (≥10%) were product administered to patient of inappropriate age (n=15), off-label use (n=11), headache (n=7), exposure via breast milk (n=5), rash (n=5), pyrexia (n=4), product use issue (i.e., product use in unapproved population; n=3), dizziness (n=3), nausea (n=3), and vaccination site pain (n=3). One death report concerned an 11-year-old female but it was not clear if she had received the vaccine or if she was exposed to other family members who received the vaccine; this report contained limited details and was difficult to interpret. The other death report concerned a 5-month-old breastfed infant who was diagnosed with TTP after the mother received

her 2nd Pfizer-BioNTech vaccine dose; symptom onset 1-day post-maternal vaccination (this report was included in the pregnancy and lactation review above).

Reviewer comment: The Pfizer-BioNTech COVID-19 vaccine is currently authorized for use in individuals age 12 years and older and the BLA has a proposed indication for use in individuals age 16 years and older. Review of VAERS data indicates that individuals younger than age 12 have received the product outside of clinical trials; no patterns of AEs were identified to suggest new safety concerns that warrant amendment to the PVP.

6.2 Data Mining Findings

Data mining of the VAERS database using Empirica Signal[1] with a data lock point of June 4, 2021, revealed the following PTs and subgroups had an increased disproportional reporting value (EB05≥2) for the Pfizer-BioNTech COVID-19 vaccine (Table 5):

Table 5: Preferred Terms with Disproportional Reporting in Empirica Signal for the Pfizer-BioNTech COVID-19 Vaccine

Preferred Term (PT)	US EB05	US Adult ≥65 years EB05	US Female EB05
Drug ineffective	1.964	2.034	1.779
Investigation	2.053	2.071	2.001
Product preparation issue	2.021	2.124	1.947
Weight	2.02	2.028	1.98

Reviewer comment: Reports with PT "drug ineffective" generally describe patients who contracted COVID-19 prior to being fully vaccinated or reports with limited details to assess timing or confirmation of COVID-19 infection or number of vaccine doses. Cases of vaccination failure might not always be reported to a spontaneous adverse event reporting system. Inferences that can be made from VAERS about COVID disease after vaccination are limited. Vaccine effectiveness is monitored through clinical trials, and post-authorization studies conducted by the sponsor. The PT "investigation" is non-specific and generally refers to investigations performed as part of work-up for signs or symptoms. The PT "product preparation issue" generally concerns reports with issues such as incorrect vaccine reconstitution or lack of reconstitution with diluent. The PT of

[1] Empirica Signal is a web-based platform that uses an automated approach to explore relationships in large datasets by generating statistical scores for combinations of products and events from drug or vaccine databases. Data mining is conducted to evaluate whether any events (i.e., MedDRA PTs) following use of a particular vaccine are disproportionally reported compared to all vaccine reports in VAERS; the threshold for signal detection is an EB05 value ≥2. (EBO5 is the lower bound of the 90% confidence limit for the Empirical Bayesian Geometric Mean). The data generated from Empirica Signal do not, by themselves, demonstrate causal associations, but the data might serve as a signal for further investigation and can be useful for hypothesis generation and exploration of potential concerns.

"weight" is non-specific and may refer to weight gain or loss in a patient or report of the patient's weight. Review of PTs with an EB05≥2 did not identify new safety concerns that need to be addressed in the PVP.

6.3 Discussion of U.S. Package Insert (USPI) Section 6.2 Post-marketing Experience

Sponsor proposed AEs for inclusion under Section 6.2 Post-marketing Experience include:

Cardiac Disorders: myocarditis and pericarditis

Gastrointestinal Disorders: diarrhea, vomiting

Immune System Disorders: severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritis, urticaria, angioedema)

Musculoskeletal and Connective Tissue Disorders: pain in extremity (arm)

OBE/DE recommends inclusion of additional PTs to Section 6.2 Post-marketing Experience for:

- Dizziness
  - Among serious reports (as of August 2, 2021), dizziness ranks in the cumulative top 10 reported PTs with 11,107 events reported. A cumulative VAERS query for the PT dizziness, run on August 3, 2021, returned 35,104 reports (26,131 [74.4%] were U.S. reports), including 3,857 (11.0%) serious reports (145 of these were death reports). There were 26,032 (74.2%) reports concerning females and 8,615 (25.5%) concerning males; 457 (1.3%) reports did not include sex. The median onset based on VAERS dates=0 days (range=0-171 days post-vaccination) and median age=42 years (range=0.1-115 years).
- Dyspnea
  - Among serious reports (as of August 2, 2021), dyspnea ranks in the cumulative top 10 reported PTs with 10,506 events reported. A cumulative VAERS query for the PT dyspnea, run on August 3, 2021, returned 19,858 reports (12,757 [64.2%] were U.S. reports), including 6,235 (31.4%) serious reports (1,102 of these were death reports). There were 14,166 (71.3%) reports concerning females and 5,421 (27.3%) concerning males; 271 (1.4%) reports did not include sex. The median onset based on VAERS dates=0 days (range=0-207 days post-vaccination) and median age=48 years (range=0.1-109 years).

7 Pharmacovigilance Plan

7.1 Summary of Pharmacovigilance Plan

The sponsor submitted a PVP proposing routine pharmacovigilance (PV), including data capture aids (DCAs) for anaphylactic reactions and VAED, and post-authorization observational and active surveillance safety studies (Table 6). There are also ongoing clinical trials.

Table 6: Summary of Safety Concerns and Planned Pharmacovigilance Activities*

Safety Concern	Actions Proposed
Important Identified Risks	
Anaphylaxis	• Routine pharmacovigilance • Data capture aid • Communication of important identified risk via label (Sections 4 - *Contraindications*, 5.1 - *Management of Acute Allergic Reactions,* Section 6 - *Adverse reactions* - and 6.2 - *Post Authorization Experience*) • Completion of C4591001: Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 mRNA vaccine candidates against COVID-19 in healthy individuals • Three post-authorization safety studies to monitor safety of BNT162b2 (C4591009, C4591011, C4591012)
Myocarditis and Pericarditis	• Routine pharmacovigilance • Three post-authorization safety studies to monitor safety of BNT162b2 (C4591009, C4591011, C4591012) • FDA will also require a safety post-marketing study to further assess these serious risks
Important Potential Risks	
Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)	• Routine pharmacovigilance • Data capture aid • Completion of C4591001: Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 mRNA vaccine candidates against COVID-19 in healthy individuals • Four post-authorization safety studies to monitor safety of BNT162b2 (C4591008, C4591009,

	C4591011, C4591012)
Missing Information	
Use in pregnancy and lactation	• Routine pharmacovigilance • Completion of C4591015: A phase 2/3, placebo-controlled, randomized, observer blind study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older • Three post-authorization safety studies to monitor safety of BNT162b2 (C4591009, C4591011, C4591022 [Pregnancy Registry study])
Vaccine effectiveness	• Routine pharmacovigilance • Completion of BNT162-01 cohort 13 (Phase 1/2 dose-escalation clinical trial): Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses • Three post-authorization vaccine effectiveness studies (C4591014: Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California • WI235284: determining RSV Burden and Outcomes in Pregnant Women and Older Adults Requiring Hospitalization. COVID-19 Amendment for COVID VE/ Sub-study 6 • WI255886: Avon Community Acquired Pneumonia Surveillance Study: A Pan- pandemic Acute Lower Respiratory Tract Disease Surveillance Study
Use in pediatric individuals <12 years of age	• Routine pharmacovigilance • Completion of C4591001 ≥12 to ≤15 years of age: Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 mRNA vaccine candidates against COVID-19 in healthy individuals. Randomized placebo-controlled study in 2,000 participants (1,000 active recipients) of 2 doses of BNT162b2 at a 21-day interval • Completion of C4591007 <12 years of age: Phase 1 open label dose-finding study to

	evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 mRNA vaccine candidate against COVID-19 in healthy children <12 years of age • One post-authorization safety study to monitor safety of BNT162b2 (C4591009)

*Adapted from sponsor's Pharmacovigilance Plan, Version 1.1 Table 46: Summary of Safety Concerns and Action Plans.

7.3 Summary of Post-authorization Safety Surveillance Studies

The sponsor proposes five post-authorization safety surveillance studies, which are summarized in the sections below. The sponsor also proposes three post-authorization vaccine effectiveness studies (C4591014, WI235284, WI255886):

- C4591014: Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California
- WI235284: Determining RSV Burden and Outcomes in Pregnant Women and Older Adults Requiring Hospitalization; COVID-19 Amendment for COVID VE/ Sub-study 6
- WI255886: Avon Community Acquired Pneumonia Surveillance Study: A Pan-pandemic Acute Lower Respiratory Tract Disease Surveillance Study

Reviewer comment: *The vaccine effectiveness study protocols were submitted to IND 19736/268 and are being reviewed by the CBER Biologics Effectiveness and Safety (BEST) team; see memorandums from CBER BEST team for study details and OBE assessment.*

7.3.1 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

The primary objective of this study is to estimate the real-world incidence of safety events of interest and other clinically significant events among U.S. healthcare workers vaccinated with the Pfizer-BioNTech COVID-19 vaccine following EUA. Secondary objectives are to evaluate whether the vaccine recipients experience increased risk of safety events of interest and other clinically significant events post-vaccination and to estimate the incidence rates of safety events of interest and other clinically significant events among sub-cohorts, such as individuals who are pregnant or immunocompromised, and stratified by age.

This prospective observational study will collect data based on participant self-report

(primarily using a secure web portal) at regular intervals for 24 months following vaccination. Events will be confirmed using medical records. This study aims to enroll at least 20,000 HCW who received a COVID-19 vaccine. Safety outcomes of interest area based on the priority list of AESI from the Brighton Collaboration's Safety Platform for Emergency Vaccines (SPEAC) Project (https://brightoncollaboration.us/priority-list-aesi-covid/; accessed 12/13/2020) and include the following (* denotes events that will only be collected if individual hospitalized):

- Neurologic: generalized convulsion/seizures, Guillain-Barré syndrome, aseptic meningitis, encephalitis/encephalomyelitis, other acute demyelinating diseases, transverse myelitis, multiple sclerosis, optic neuritis, Bell's palsy
- Immunologic: anaphylaxis, vasculitides*, arthritis/arthralgia, multisystem inflammatory syndrome (in adults), Kawasaki disease, fibromyalgia, autoimmune thyroiditis
- COVID-19: severe COVID-19 disease*, microangiopathy*, heart failure and cardiogenic shock*, stress cardiomyopathy*, coronary artery disease*, arrythmia*, deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, limb ischemia*, hemorrhagic disease*, acute kidney injury*, liver injury, Chillblain-like lesions, single organ cutaneous vasculitis*, erythema multiforme*
- Cardiac: myocarditis, pericarditis, acute myocardial infarction
- Hematologic: thrombocytopenia, disseminated intravascular coagulation
- Other: pregnancy outcomes, death, narcolepsy and cataplexy, non-anaphylactic allergic reactions

Data analysis will include descriptive statistics of vaccination and baseline characteristics, number and incidence rate for each safety event of interest will be calculated overall and within subgroups of interest. Qualitative comparisons will be made using hospitalization rates among non-vaccinated HCW enrolled in the HERO registry and external sources of background event rates. A self-matched comparative analysis will then be performed for events that appear to be associated with vaccination and that are amenable to self-matched analysis (e.g., adequate case counts, known risk interval).

The proposed study milestones are:

Interim report submission: June 30, 2021; December 31, 2021; June 30, 2022; December 31, 2022

Final study report submission: December 31, 2023

<u>Reviewer comment:</u> This study was proposed in the original EUA submission (EUA 27034/0) and the final study protocol was submitted to EUA 27034/68; OBE/DE reviewed the final study protocol and provided comments to the sponsor. In addition, the sponsor submitted an interim statistical analysis plan (SAP) and a protocol amendment (IND 19736/324) to expand the study population to include HCW families and community members, update recruitment strategies, and provide additional details

regarding the clinical event ascertainment process. The protocol amendment and SAP were reviewed by OBE/DE and are acceptable. Please see previous review memorandums for additional details.

7.3.2 C4591009: A non-interventional post-approval safety study of the Pfizer--BioNTech COVID-19 mRNA vaccine in the United States

The primary objective of this study is to estimate the relative risk (RR) or prevalence ratio of safety events of interest following receipt of at least one dose of the Pfizer-BioNTech COVID-19 vaccine in the overall study population and in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19. Secondary objectives are to describe the proportion of individuals receiving at least one dose and a complete dose series, the timing and type of second dose of COVID-19 vaccine, and the baseline characteristics of individuals who receive at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared to those who do not receive any COVID-19 vaccine doses.

This is a retrospective cohort study comparing vaccinated individuals with concurrent unexposed comparators using claims and electronic health record data from partners in the Sentinel System. Safety events of interest will be aligned with events being monitored in the rapid cycle analysis of COVID-19 vaccines in the FDA's BEST system and CDC's VSD. The study will estimate incidence rates or incidence/prevalence proportions for each safety event of interest for matched exposed and unexposed cohorts; comparative analyses will also estimate hazard ratios or incidence rate ratios and 95% CI within propensity score-matched cohorts. Individuals of all ages will be included in the descriptive analysis of vaccine utilization while the safety analysis will be limited to individuals within the age-indicated population for the Pfizer-BioNTech COVID-19 vaccine. The study period will extend a minimum of three years post-EUA

The proposed study milestones are:

Final protocol submission: August 31, 2021

Monitoring report submission: October 31, 2022

Interim report submission: October 31, 2023

Final study report submission: October 31, 2025

<u>Reviewer comment:</u> This study was proposed in the EUA submission to expand the Pfizer-BioNTech COVID-19 vaccine indication to pediatric individuals age 12-15 years (EUA 27034/132); a study protocol synopsis was submitted with the BLA.

7.3.3 C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 vaccine in the U.S. Department of Defense population following Emergency Use Authorization

The primary objective of this study is to assess whether individuals and sub-cohorts of interest (i.e., pregnant women, immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 vaccine, and individuals with prior SARS-CoV-2 infection) in the Department of Defense (DoD) military health system (MHS) experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine. Secondary objectives are to characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the DoD MHS.

This active safety surveillance study will utilize a rapid-cycle, longitudinal, observational cohort study design to assess real-world safety of the Pfizer-BioNTech COVID-19 vaccine using a self-controlled risk interval design and a cohort design with two comparator populations (2018/2019 season influenza vaccine recipients and unvaccinated matched controls). Safety events of interest are aligned with AESIs from the Brighton Collaboration's SPEAC Project, FDA, and CDC's Advisory Committee on Immunization Practices (ACIP) enhanced safety monitoring recommendations. A stepwise data analysis process will include signal detection, evaluation, and verification. The study will use coding and medical record data from the DoD MHS Data Repository and will be conducted for 30-months post-EUA.

The proposed study milestones are:

Interim report submissions: June 30, 2021; December 31, 2021; June 30, 2022; December 31, 2022

Final study report submission: December 31, 2023

<u>Reviewer comment:</u> This study was proposed in the original EUA submission (EUA 27034/0). The final study protocol was submitted to EUA 27034/68 and reviewed by the CBER BEST team. An IR response (EUA 27034/186) indicated that the start date for C4591011 is delayed due to a change in study collaborators and the first interim report will be submitted by December 31, 2021 rather than June 30, 2021. Please see previous review memorandums for additional details.

7.3.4 C4591012: 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

The primary objective of this study is to assess whether individuals and sub-cohorts of interest (i.e., immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 vaccine, and individuals with prior SARS-CoV-2 infection) in the Veterans Health Administration

(VHA) system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine. Secondary objectives are to characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA.

This active safety surveillance study will utilize a rapid-cycle, longitudinal, observational cohort study design to assess real-world safety of the Pfizer-BioNTech COVID-19 vaccine using a self-controlled risk interval design and an active comparator design (2014/2015 through 2018/2019 seasonal influenza vaccine recipients). Safety events of interest are aligned with AESIs from the Brighton Collaboration's SPEAC Project, FDA, and CDC's ACIP enhanced safety monitoring recommendations. A stepwise data analysis process will include signal detection, evaluation, and verification. The study will use coding and medical record data from the VHA Corporate Data Warehouse which is an integrated electronic medical record system and will be conducted for 30-months post-EUA.

The proposed study milestones are:

Interim report submissions: June 30, 2021; December 31, 2021; June 30, 2022; December 31, 2022

Final study report submission: December 31, 2023

<u>Reviewer comment:</u> This study was proposed in the original EUA submission (EUA 27034/0). The final study protocol was submitted to EUA 27034/68 and reviewed by the CBER BEST team. An IR response (EUA 27034/186) indicates that the protocol will be revised to incorporate CBER BEST team comments regarding the addition of a contemporary unvaccinated comparator cohort for signal evaluation; a revised protocol will be submitted by August 31, 2021. Please see previous review memorandums for additional details.

7.3.5 C4591022: 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 (OTIS)/Mother To Baby Pregnancy Registry

The primary objective of this pregnancy registry study is to assess whether pregnant women in the Organization of Teratology Information Specialists (OTIS) Pregnancy Registry receiving the Pfizer-BioNTech COVID-19 vaccine experience increased risk of pregnancy and infant safety outcomes. The secondary objective is to characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among pregnant women in the OTIS registry.

This prospective, observational cohort pregnancy registry study will utilize two comparator groups: 1) pregnant women who received an influenza or Tdap (tetanus, diphtheria, and acellular pertussis) vaccine during pregnancy and 2) pregnant women who received no vaccines during pregnancy. The study aims to enroll 1800 pregnant women over a 3-year recruitment period. Pregnancy and infant safety outcomes will include major congenital malformations, spontaneous abortion, stillbirth, preterm

delivery, small for gestational age, and small for age postnatal growth to one year of age. Data will be collected using maternal interviews, medical record review, and a pregnancy exposure diary. Data analysis will include descriptive statistics, birth prevalence rates and incidence rates, and risk estimates.

The proposed study milestones are:

Final protocol submission: July 1, 2021

Interim report submissions: January 31, 2022; January 31, 2023; January 31, 2024; January 31, 2025

End of data collection: December 31, 2024

Final study report submission: December 1, 2025

Reviewer comment: This pregnancy registry study will be a post-marketing commitment (PMC).

8 DE Assessment of Sponsor's Pharmacovigilance Plan

8.1 Important Identified Risk: Anaphylaxis

The risk of anaphylaxis was recognized early in the post-authorization time period and information was added to the EUA Fact Sheets for healthcare providers and recipients and caregivers. One BNT162b2-related-SAE of anaphylactoid reaction occurred in a clinical trial (C4591001) participant who originally received placebo and then received BNT162b2 after unblinding. This individual had an ongoing medical history of drug hypersensitivity and food and seasonal allergies and had onset 2-days post-1st dose of BNT162b2; she self-administered an epinephrine pen and symptoms resolved the same day. In addition, the sponsor's summary of post-authorization AE reports identified 1,002 cases of anaphylaxis that met the Brighton Collaboration (BC) definition level 1 (highest level of certainty) through 4 (reported event with insufficient evidence to meet case definition), including nine fatal events. A VAERS search for reports of anaphylaxis returned 1,034 reports, including 524 serious reports and 12 death reports; there were no patterns suggestive of any new safety signals.

The important identified risk of anaphylaxis, which can be fatal or life-threatening, will be monitored through routine pharmacovigilance activities, including a data capture aid to identify relevant clinical information, and post-authorization safety studies. This safety concern has labeling proposed in the following sections of the USPI:

- Section 4 Contraindications
- Section 5 Warnings and Precautions, 5.1 Management of Acute Allergic Reactions
- Section 6 Adverse Reactions

Reviewer comment: The proposed PVP is adequate to monitor the risk of anaphylaxis.

8.2 Important Identified Risk: Myopericarditis and Pericarditis

During the post-authorization period, myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine was reported to VAERS. Myocarditis and pericarditis emerged as a safety signal in VAERS, and there are ongoing analyses for further characterization of these risks. CDC issued clinical considerations regarding myocarditis and pericarditis after receipt of mRNA COVID-19 vaccines among adolescents and young adults in May 2021. Myocarditis and pericarditis following mRNA COVID-19 vaccines was discussed at the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) and CDC Advisory Committee on Immunization Practices (ACIP) meetings in June 2021. The EUA Fact Sheet was revised on June 25, 2021 to add a Warning for myocarditis and pericarditis and the PVP was amended to include myocarditis and pericarditis as important identified risks. The sponsor's PVP indicates that a mechanism of action has not been established for how the vaccine could cause myocarditis and pericarditis, however potential hypotheses are related to an immune stimulated response, a general systemic inflammatory response, or a hypersensitivity response. The revised PVP (Version 1.1) also included post-authorization data for myocarditis and pericarditis among individuals 16 years of age and older through June 18, 2021. As per the sponsor, there was a total of 823 reports, including 490 reports of myocarditis and 372 reports of pericarditis. A VAERS search for reports of myopericarditis returned 1,023 reports (1,012 were U.S. reports), including 809 serious reports (seven were death reports concerning six unique individuals). As described in the O/E analysis given a 7-day risk window (Tables 3 and 4), the reporting rate and RR is elevated in age groups under 30 years, with more cases occurring after dose 2. The reporting rate and RR was higher among males than females for almost all age groups.

Monitoring for myocarditis and pericarditis is ongoing and includes the following activities:

- Continued passive surveillance using VAERS
- Vaccine Safety Datalink (VSD) analyses for safety signals
- Ongoing Sponsor passive surveillance using worldwide adverse events data
- Ongoing Sponsor active surveillance studies

In addition, a safety post-marketing requirement (PMR) under FDAAA is warranted to further characterize the serious risk of myopericarditis.

This safety concern has labeling proposed in the following sections of the USPI:

- Section 5 Warnings and Precautions
- Section 6 Adverse Reactions

<u>Reviewer comment:</u> The sponsor's proposed PVP and FDA required post-marketing study is adequate to monitor and further assess the risk of myocarditis and pericarditis including long-term follow up. Please see PVP addendum memo for review of the safety PMR.

8.3 Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Vaccine-associated enhanced disease (VAED) is a modified and/or severe presentation of an infectious disease in individuals exposed to a wild-type pathogen following receipt of a vaccine designed to prevent infection (Munoz, 2021). The clinical manifestations of VAED are within the spectrum of natural disease and are difficult to separate from vaccine failure; there are no specific biomarkers or histopathologic findings for VAED (Munoz, 2021). In addition, there can be multiple pathophysiologic pathways that could lead to VAED/VAERD in general, such as immune complex mediated enhanced disease, cellular immunity in enhanced respiratory disease, antibody mediated enhanced disease, cytokine activation, or vaccine-induced enhancement of infection acquisition (Munoz, 2021). The sponsor cites VAED as a theoretical risk based on animal models of related betacoronaviruses, including SARS-CoV-1 and MERS-CoV, and disease enhancement that was seen in vaccinated children following infection with natural virus after receipt of inactivated respiratory syncytial virus vaccine. Data from the blinded placebo-controlled follow-up period in Study C4591001 show one confirmed case of post-vaccination severe COVID-19 compared to 31 confirmed cases in the placebo group. No post-authorization AE reports have been identified as cases of VAED/VAERD. The important potential risk of VAED will be monitored through routine pharmacovigilance activities, including a data capture aid to identify relevant clinical information, and post-authorization safety studies.

Reviewer comment: The favorable balance of confirmed cases of severe COVID-19 in BNT162b2 vs placebo recipients in Study C4591001 is reassuring. The proposed PVP is adequate to monitor the potential risk of VAED and VAERD.

8.4 Missing Information: Use in pregnancy and lactation

Pregnant women were excluded from the pivotal clinical trial and the safety profile of the Pfizer-BioNTech COVID-19 vaccine in pregnant or lactating women is not known. Post-authorization data from the sponsor's safety database and a VAERS search did not identify any patterns suggesting new safety concerns. Missing information regarding the use of the product during pregnancy and lactation will be monitored through routine pharmacovigilance activities, a clinical trial, and post-authorization safety studies, including a Pregnancy Registry study which will be a PMC. The lack of safety data will be communicated in product labeling (Section 8.1 Pregnancy and 8.3 Lactation).

Reviewer comment: The proposed PVP is adequate to monitor for use in pregnancy and lactation.

8.5 Missing Information: Vaccine effectiveness

Real-world vaccine effectiveness of the Pfizer-BioNTech COVID-19 vaccine outside of clinical trials and in larger and more diverse populations is not known. Post-

authorization data from the sponsor's safety database identified 16 cases of vaccination failure out of 42,086 total AE cases reported cumulatively to February 28, 2021. The sponsor's review of these cases did not reveal any new safety signals associated with the lack of vaccine effectiveness. In addition, a VAERS search returned 1,788 reports that included the PT vaccination failure (n=254) and/or drug ineffective (n=1,565); 31 reports contained both PTs; there were no patterns suggestive of any safety signals. Missing information regarding real-world vaccine effectiveness will be monitored through routine pharmacovigilance activities and post-authorization real-world vaccine effectiveness studies. Data on vaccine efficacy in clinical trials will be communicated in product labeling (Section 14 Clinical Studies).

Reviewer comment: The proposed PVP is adequate to monitor vaccine effectiveness.

8.6 Missing Information: Use in pediatric individuals <12 years of age

Pediatric individuals <12 years of age were excluded from the pivotal clinical trial and the safety profile in this population is not known. Post-authorization data from the sponsor's safety database revealed 34 cases concerning 132 AEs; review of PTs did not reveal new safety concerns. A VAERS search returned 273 reports concerning individuals <12 years of age and did not suggest any patterns concerning for any new safety signals. Missing information regarding pediatric individuals <12 years of age will be monitored through routine pharmacovigilance activities and a post-authorization safety study. There are also ongoing clinical trials. The lack of safety data will be communicated in product labeling (Section 8.4 Pediatric Use).

Reviewer comment: The proposed PVP is adequate to monitor use in individuals <12 years of age.

9 DE Conclusions

Based on review of available data, there is a new safety signal for myopericarditis from post-authorization safety surveillance which warrants a FDAAA Title IX PMR safety study to assess the important identified risk of myopericarditis. Please see PVP addendum memo for review of the safety PMR. The sponsor's proposed Pregnancy Registry study (C4591022) will be a PMC. In addition, the safety of BNT162b2 can be monitored through routine PV activities, risk communication through labeling, and the additional post-authorization safety studies proposed by the sponsor.

10 DE Recommendations

Should the product be approved, based on the review of the clinical trial safety data, and the post-authorization safety data, OBE/DE recommends the following actions:

- **Routine pharmacovigilance** in accordance with adverse event reporting regulations under 21 CFR 600.80, as per the sponsor's proposed PVP.

- **Post-marketing requirement (PMR) safety study** under Section 505(o) of the FDCA (amended by FDAAA, Title IX, Section 901), to assess the serious risk of myopericarditis. (Please see PVP addendum memo for review of the safety PMR.)
- **Post-marketing commitment (PMC) safety study** for a pregnancy registry (C4591022) to assess whether pregnant women receiving the Pfizer-BioNTech COVID-19 vaccine experience an increased risk of pregnancy and infant safety outcomes compared to two comparator groups.
- **Voluntary post-marketing studies**: Post-EUA studies that continue as voluntary studies will be followed through updates in periodic safety update reports (PSURs).

OBE/DE also recommends inclusion of the following AEs to the USPI, Section 6.2 Post-marketing Experience: dizziness and dyspnea.

At this time, the available safety data do not suggest a safety concern that would require a REMS. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

11 References

Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020. MMWR Morb Mortal Wkly Rep 2021;70:46–51. DOI: http://dx.doi.org/10.15585/mmwr.mm7002e1

Gee J, Marquez P, Su J, et al. First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021. MMWR Morb Mortal Wkly Rep 2021;70:283–288. DOI: http://dx.doi.org/10.15585/mmwr.mm7008e3

Gubernot D, Jazwa A, Niu M, Baumblatt J, U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021 Jun 23;39(28):3666-3677. PMID: 34088506.

Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Haberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. BMJ. 2019;364:l869.

Munoz FM, Cramer JP, Dekker CL, Dudley MZ, Graham BS, Gurwith M, Law B, Perlman S, Polack FP, Spergel JM, Van Braeckel E, Ward BJ, Didierlaurent AM, Lambert PH; Brighton Collaboration Vaccine-associated Enhanced Disease Working Group. Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2021 May 21;39(22):3053-3066. doi: 10.1016/j.vaccine.2021.01.055. Epub 2021 Feb 23. PMID: 33637387; PMCID: PMC7901381.

Myocarditis Brighton Collaboration Definition (Pandemic Emergency Response Process_Draft Release), Version 1.4.2; May 30, 2021. Available at: https://brightoncollaboration.us/wp-content/uploads/2021/07/Myocarditis-CD_Version_1.4.2_30.May_.2021__LOC_ALL__FINAL.POSTING.pdf

Roth, G. A., Mensah, G., Johnson, C.O., Addolorato, G., Journal of the American College of Cardiology J Am Coll Cardiol. 2020 Dec 22; 76(25): 2982–3021. PMID: 33309175.

Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, de Souza Brito G, Heininger U, Imoukhuede B, Khamesipour A, Erlewyn-Lajeunesse M, Martin S, Mäkelä M, Nell P, Pool V, Simpson N; Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5675-84. doi: 10.1016/j.vaccine.2007.02.064. Epub 2007 Mar 12. PMID: 17448577.

Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. JAMA. 2021 Mar 16;325(11):1101-1102. doi: 10.1001/jama.2021.1967. PMID: 33576785

Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Epidemiology (OBE)
Division of Epidemiology (DE)

PHARMACOVIGILANCE PLAN REVIEW: ADDENDUM MEMORANDUM

From:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE) Kerry Welsh, MD Medical Officer, Analytic Epidemiology Branch (AEB)
To:	Ramachandra Naik, PhD Chair, Review Committee Office of Vaccines Research and Review (OVRR), CBER, FDA
Through:	Manette Niu, MD Branch Chief, AEB DE, OBE, CBER, FDA Narayan Nair, MD Division Director, DE OBE, CBER, FDA
Subject:	Review of Pharmacovigilance Plan – Addendum memo
Sponsor:	Pfizer
Product:	COMIRNATY; BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)
BLA Number:	125742/0
Proposed Indication:	Active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals ≥16 years of age.
Submission Date:	May 18, 2021
Action Due Date:	January 16, 2022

1 Objectives and Scope

The sponsor's proposed pharmacovigilance plan (PVP), clinical safety database and post-authorization safety data were reviewed in the OBE/DE Pharmacovigilance Plan Review Memorandum, dated August 6, 2021 (OBE/DE primary reviewer: Deborah Thompson, MD). This addendum memo serves to provide review updates, including additional VAERS analysis for adverse events of special interest, and new information on sponsor proposed postmarketing safety studies, and final OBE/DE recommendations for postmarket safety monitoring for COMIRNATY.

2 Vaccine Adverse Event Reporting System Data

FDA post-authorization safety data was previously summarized in section 6 of OBE/DE Pharmacovigilance Plan Review Memorandum, dated August 6, 2021. A COVID-19 Vaccine Safety Update[1] from the European Medicines Agency (EMA) prompted further VAERS analysis of the following adverse events of special interest (AESI): erythema multiforme; glomerulonephritis and nephrotic syndrome; menstrual disorders.

- Erythema multiforme (EM), Stevens-Johnson Syndrome, and toxic epidermal necrolysis:
  A query[2] of the VAERS database on August 16, 2021, retrieved 194 reports of which there were 53 U.S. reports. Among U.S. reports (n = 53), there were 12 serious reports including 1 death:
    - The patient that died (VAERS ID 1034116) was a 58 year old female who presented with 3 - 4 days of extensive rash with skin sloughing 11 days after vaccination. Skin biopsy was compatible with toxic epidermal necrolysis. She died [redacted] days after vaccination.

  Cases involved 29 females, 23 males and sex was unknown in one case. Median age was 56 years (range 13 – 98 years, unknown for 5 cases). Interval to onset of symptoms post vaccination was 2 days (range 0 – 45 days, unknown for 3 cases).

- Glomerulonephritis and nephrotic syndrome:
  A query[3] of the VAERS database on August 16, 2021, retrieved 175 reports of which there were 57 U.S. reports. Among U.S. reports (n = 57), there were 35 serious reports. There were no deaths. Cases involved 24 females, 32 males and sex was not reported in one case. Median age was 40 years (range 12 – 88

[1] https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-spikevax-previously-covid-19-vaccine-moderna-11-august-2021_en.pdf

[2] Preferred Terms (PTs) for query: ERYTHEMA MULTIFORME;STEVENS-JOHNSON SYNDROME;TOXIC EPIDERMAL NECROLYSIS

[3] PTs for query: ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE;C3 GLOMERULOPATHY;FIBRILLARY GLOMERULONEPHRITIS;FOCAL SEGMENTAL GLOMERULOSCLEROSIS;GLOMERULONEPHRITIS;GLOMERULONEPHRITIS ACUTE;GLOMERULONEPHRITIS CHRONIC;GLOMERULONEPHRITIS MEMBRANOPROLIFERATIVE;GLOMERULONEPHRITIS MEMBRANOUS;GLOMERULONEPHRITIS MINIMAL LESION;GLOMERULONEPHRITIS PROLIFERATIVE;GLOMERULONEPHRITIS RAPIDLY PROGRESSIVE;GOODPASTURES SYNDROME;GRANULOMATOSIS WITH POLYANGIITIS;HENOCH-SCHONLEIN PURPURA;HENOCH-SCHONLEIN PURPURA NEPHRITIS;IGA NEPHROPATHY;IGM NEPHROPATHY;MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS;MICROSCOPIC POLYANGIITIS;NEPHRITIC SYNDROME;NEPHRITIS ALLERGIC;NEPHRITIS;NEPHRITIS INTERSTITIAL;NEPHROTIC SYNDROME

years, unknown for 2 cases). Interval to onset of symptoms post vaccination was 2.5 days (range 0 – 48 days, unknown for 3 cases).

- Menstrual disorders:
  A query[4] of the VAERS database on August 16, 2021, retrieved 7249 reports of which there were 3327 U.S. reports. Twenty-eight U.S. reports were excluded because sex was reported as male, or sex was not reported. Among U.S. cases in females only (n = 3299), there were 85 serious reports. There were no deaths. Median age was 37 years (range 12 – 74 years, unknown for 107 cases). Interval to onset of symptoms post vaccination was median 3 days (range 0 – 154 days, unknown for 158 cases).

Reviewer comment: Note that the above analysis is based on case counts retrieved from automated queries, and individual cases were not manually reviewed. Limitations of passive surveillance data include missing/incomplete data and unconfirmed diagnoses. In the context of 201,577,973 doses of Pfizer-BioNTech COVID-19 Vaccine administered[5], there are no new safety signals identified from the above analysis of VAERS data at this time. Based on the above query results, there were few U.S. reports for erythema multiforme (n = 53 U.S.) and glomerulonephritis and nephrotic syndrome (n = 57 U.S. reports). Majority of the reports of menstrual disorders were non-serious reports. Menstrual disorders are common in the general population and can occur without an underlying medical condition. OBE/DE will continue safety monitoring for adverse events after COMIRNATY. We will review any additional information on these AESIs from EMA when available.

3 Serious risks: myocarditis and pericarditis, and subclinical myocarditis

Myocarditis and pericarditis: Post-authorization safety data (previously described in section 6 of OBE/DE Pharmacovigilance Plan Review Memorandum, dated August 6, 2021) has identified serious risks for myocarditis and pericarditis after COMIRNATY, with increased risk in males under 30 years of age, particularly following the second dose, and onset of symptoms within 7 days following vaccination. Authorized EUA Fact Sheets were updated on June 25, 2021, to include a new Warning about myocarditis and pericarditis.

Subclinical myocarditis: Incidence of subclinical myocarditis and potential long-term sequelae following COMIRNATY are unknown. A previous study[6] of smallpox vaccine

[4] PTs for query: ABNORMAL UTERINE BLEEDING;ABNORMAL WITHDRAWAL BLEEDING;ANOVULATORY CYCLE;BLEEDING ANOVULATORY; DELAYED MENARCHE;DYSMENORRHOEA;INTERMENSTRUAL BLEEDING;MENSTRUAL DISORDER;MENSTRUAL DISCOMFORT; MENSTRUATION IRREGULAR;PREMENSTRUAL DYSPHORIC DISORDER;PREMENSTRUAL PAIN;PREMENSTRUAL SYNDROME;WITHDRAWAL BLEED; AMENORRHOEA; HYPOMENORRHOEA;MENSTRUATION DELAYED; OLIGOMENORRHOEA;HEAVY MENSTRUAL BLEEDING; MENOMETRORRHAGIA; POLYMENORRHAGIA; POLYMENORRHOEA

[5] CDC COVID Data Tracker accessed on August 18, 2021 https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total

[6] Engler RJ, et al. A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination. PLoS One. 2015;10(3):e0118283

suggested an incidence of possible subclinical myocarditis (based on cardiac troponin T elevations) 60-times higher than the incidence rate of overt clinical myocarditis.

FDA information request dated July 28, 2021, asked the sponsor to propose postmarketing observational safety study(ies) to assess myocarditis and pericarditis following administration of COMIRNATY to quantify the magnitude of risk by age, sex, and dose; include follow up cases (e.g., via a registry) for recovery status and long-term sequelae; and propose plans to characterize subclinical cases of myocarditis. The sponsor's proposed plans were reviewed (responses to Information Requests dated July 28, 2021, and August 10, 2021) and recommendations for proposed safety postmarketing requirements/commitments (PMRs/PMCs) as well as CBER Sentinel Sufficiency assessment were presented to the CBER Safety Working Group (SWG) on August 12, 2021.

4 Sponsor proposed post-authorization/postmarketing safety studies

The safety surveillance studies proposed by the Sponsor were previously reviewed in section 7.3 of OBE/DE Pharmacovigilance Plan Review Memorandum, dated August 6, 2021. Additional information provided by the sponsor is summarized below.

<u>Studies to assess risks of myocarditis, pericarditis and subclinical myocarditis</u>

- C4591021 and C4591021 substudy (EU): *Post Conditional Approval Active Surveillance Study Among Individuals in Europe*
    - C4591021 is a retrospective cohort study and the C4591021 substudy is a natural history cohort study within a retrospective cohort study. The substudy plans to collect follow-up for treatment for myocarditis and pericarditis, clinical outcomes, and recovery. The data source comprises of electronic healthcare databases in Netherlands, Norway, United Kingdom, Italy and Spain. The sponsor estimates that the EU databases will capture approximately 4.1 million individuals ≤ 30 years of age with exposure to COMIRNATY. The final protocol for study C4591021 was approved by the EMA on June 24, 202, and this protocol was submitted to FDA for review on August 11, 2021 and is currently under review.[7]
- Prospective cohort registry study for long term follow-up, in collaboration with Pediatric Heart Network (PHN). PHN is a multi-center consortium of hospitals across U.S. and Canada that conducts research for congenital and pediatric-acquired heart disease. The National Institutes of Health (NIH)/National Heart, Lung and Blood Institute (NHLBI) provides funding for PHN. The sponsor identified approximately 130 patients (as of August 2021), who presented to PHN

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0118283

[7] Note that review of study protocols are documented in separate protocol review memorandums.

sites after receiving a COVID-19 vaccine and were diagnosed with myocarditis. The sponsor states that, "additional patients continue to present and could be enrolled." Projected sample size and statistical analysis plan will be provided upon submission of the final study protocol on November 30, 2021. In accordance with FDA recommendations, the sponsor has agreed to follow subjects prospectively for 5 years. The objectives of the study include:

  - Characterize the clinical course of acute post-vaccine myocarditis
  - Characterize potential long-term sequelae and quality of life
  - Compare long-term effects of post-vaccine myocarditis with those of nonvaccine myocarditis, including myocarditis arising in COVID-infected persons
  - Identify possible risk factors for post-vaccine myocarditis (including age, sex, race, ethnicity, obesity, and other factors)

- Plans by Sponsor to characterize subclinical cases of myocarditis:
  - The sponsor has expressed challenges in proposing a potential prospective study of subclinical myocarditis because of the absence of a definition of subclinical myocarditis and unknown background incidence of troponin abnormalities. As an initial step, the sponsor plans to determine the background rate of abnormal troponin levels by analyzing troponin I levels in samples of stored sera (drawn <1 year ago) in 12-30-year-old individuals participating in BNT162b2 studies, prior to receipt of BNT162b2 (i.e., either at baseline, or at any visit for placebo recipients). Three thousand samples, stratified in the 12-17, 18-24 and 25-30 years age group, will be analyzed (there is a 95% probability of observing one abnormal result amongst the overall sample if the background rate of abnormality is 0.1%). The sponsor anticipates this analysis to be completed by the end of December 2021.
  - The sponsor has proposed modifications to the following two trials to obtain a serum sample for storage and potential future troponin testing, at baseline and 2-5 days after the second or third dose of BNT162b2:
    - Study C4591007: proposed addition of 750 participants 5 to <12 years of age (randomized 2:1 to receive BNT162b2 10 µg or placebo) and 500 participants 12-15 years of age (open label receipt of BNT162b2 30 µg).
    - C4591031 substudy: proposed addition of a new substudy of 1000 subjects with documented receipt of 2 prior 30 µg doses of BNT162b2 (the second dose received at least 6 months ago), 16 to 30 years of age (randomized 1:1 in a crossover design to receive 30 µg BNT162b2 or placebo at baseline and the alternative 4 weeks later).
  - As per the sponsor, "*Assuming that subclinical myocarditis can be defined on the basis of elevated troponin I, and that the baseline analysis indicates that such a study is feasible, we will consider C4591031 to be the*

prospective study to assess the incidence of subclinical myocarditis following vaccination in individuals ≥16 years. If the sample size of 1000 is insufficient, it will be increased through a protocol amendment."

5 CBER Safety Working Group (SWG) concurrence with proposed safety postmarketing requirements/commitments (PMRs/PMCs)

Based on review of available data, there are known risks for myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis, which warrant PMR safety studies to assess these serious risks. The CBER Sentinel Program was deemed to be insufficient to assess the serious risks of myocarditis and pericarditis and subclinical myocarditis for the following reasons (please also see Sentinel Sufficiency memorandum):

- At the time of BLA approval, the data sources in the CBER Sentinel Program are not sufficient to identify the outcomes due to lack of sufficient power to assess the magnitude of risk in patients 12-30 years of age.
- In addition, CBER Sentinel Program is not sufficient to follow up cases for recovery status and long-term sequelae of myocarditis and pericarditis, or for identification and characterization of subclinical myocarditis cases.

Furthermore, the FDA and applicant have agreed upon safety studies as PMCs to (a) assess safety in pregnant women and, (b) an active surveillance study in the Veteran's Affair Health System database, which includes sub-cohorts of interest (i.e., immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose Pfizer vaccine, and individuals with prior SARS-CoV-2 infection).

During a meeting on August 12, 2021, the CBER Safety Working Group concurred with the review team's proposed PMRs/PMCs:

- Postmarketing requirements (PMR) under Section 505(o) of Federal Food, Drug, and Cosmetic Act (FDCA) to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis:
    1. Epidemiologic studies using large electronic healthcare databases to evaluate the occurrence of myocarditis and pericarditis
        a) US – Sentinel system (C4591009)
        b) EU – active surveillance study (C4591021 and C4591021 substudy)
    2. Registry for long-term follow-up (in collaboration with Pediatric Heart Network)
    3. Prospective study to assess the incidence of subclinical myocarditis following vaccination
- Postmarketing commitments (PMCs):

1. Pregnancy registry study to assess pregnancy and infant outcomes after exposure to COMIRNATY during pregnancy among pregnant women aged 18 years or older[8] who reside in the US or Canada. (C4591022)
2. Randomized controlled trial (RCT) in pregnant women (C4591015)
3. Active safety surveillance study among persons in the Veteran's Affairs Health System (C4591012)

The sponsor was notified of the above PMRs/PMCs in an Information Request (IR) dated August 13, 2021.

Updates since August 12, 2021 SWG meeting:

- During the SWG meeting, there were questions raised regarding the feasibility of completing the RCT in pregnant women (C4591015), as planned, considering CDC's recommendation[9] of COVID-19 vaccination for all people 12 years and older, including people who are pregnant. In further communication with the sponsor, Pfizer described this as a global study that included sites outside the U.S. The Sponsor acknowledged challenges with enrollment due to recommendations for immunization of pregnant women in most participating countries, which may preclude them from reaching the full target enrollment for 700 subjects. As of August 13, 2021, enrollment included 259 subjects, and the sponsor anticipated enrollment for approximately 450 subjects by December 2021. The Sponsor's Internal Review Committee met on August 5, 2021, to review reactogenicity and safety data through 7 days after the second dose and recommended that the study continue. At this time, Pfizer plans [redacted].

  Upon further discussion between OVRR and OBE, it was decided not to include the RCT in pregnant women as a PMC at this time. The study will continue under IND. OBE defers to OVRR as the lead reviewer for this clinical trial.

- The SWG had concurred on the need for PMR(s) to further assess subclinical myocarditis, but additional details on study design were not available at the time of the SWG meeting. Since the SWG meeting, OVRR had further communication with the sponsor and, the sponsor proposed protocol modifications to two clinical trials (studies C4591007 and C4591031) to assess subclinical myocarditis. OBE defers to OVRR as the lead reviewer for these clinical trial PMRs:
  - 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

[8] The pregnancy registry will be in collaboration with the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry. The final protocol was submitted on July 1, 2021, is currently under review.

[9] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html#anchor_1628692562866

- 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 to 30 years of age

- OBE and OVRR are in agreement with the following PMC for a vaccine effectiveness study: Study C4591014, entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California." DE defers to OBE/IOD as the lead reviewer of real-world evidence (RWE) for vaccine effectiveness.

- OVRR included the following clinical trial as a PMC: An evaluation of the immunogenicity and safety of lower dose levels of COMIRNATY in individuals 12 through <30 years of age enrolled in Study C4591007. OBE defers to OVRR as the lead reviewer for this clinical trial PMC.

6 DE Recommendations

Should the product be approved, based on the review of the clinical trial safety data, and the post-authorization safety data, OBE/DE recommends the following pharmacovigilance activities:

- **Routine pharmacovigilance** in accordance with adverse event reporting regulations under 21 CFR 600.80, as per sponsor's proposed PVP (version 1.1).
- **Postmarketing requirement (PMR) safety studies** under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) 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. 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).

The following clinical trials to assess subclinical myocarditis will be under the lead review of OVRR:

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 to 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 (OTIS)/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 sponsor 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 (REMS).

Please see the approval letter for study milestone dates.
Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Epidemiology (OBE)

REAL WORLD EVIDENCE BLA MEMORANDUM

From:	Yun Lu, PhD Mathematical Statistician Analytics and Benefit-Risk Assessment Team (ABRA) Office of Biostatistics and Epidemiology (OBE) CBER, FDA
To:	Ramachandra Naik, PhD Chair of the Review Committee Office of Vaccines Research and Review
Through:	Richard Forshee, PhD Acting Deputy Director, OBE CBER, FDA
Subject:	Review of Pharmacovigilance Plan, Real World Post-Authorization Effectiveness Protocol C4591014, Post-Authorization Safety Protocols C4591009, C4591021, Amendment 30, Amendment 42, Amendment 51
Sponsor:	BioNTech RNA Pharmaceuticals GmbH/Pfizer, Inc.
Product:	COMIRNATY; Pfizer-BioNTech COVID-19 Vaccine*
Application Type/Number:	BLA STN 125742/0
Proposed Indication:	Prevention of COVID-19 in individuals 16 years of age and older
Submission Date:	May 18, 2021

*The product was also referred to as BNT162b2 in the clinical development

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the real world post-authorization vaccine effectiveness protocols C4591014, post-authorization vaccine safety protocols C4591009 and C4591021 for Pfizer-BioNTech coronavirus disease 2019 (COVID-19) Vaccine COMIRNATY.

Materials Reviewed

- Pharmacovigilance Plan, Version 1.1 (STN 125742/0.20; received July 29, 2021)
- Response to CBER 28 July 2021 Information Request Regarding Post-marketing Safety Study(ies) (STN 125742/0.30; received August 3, 2021)
- Response to CBER 10 August 2021 Information Request Regarding Post-marketing Safety Studies (STN 125742/0.42; received August 11, 2021)
- Response to CBER 13 August 2021 Information Request Regarding Safety-Related Postmarketing Requirement/Postmarketing Commitment Studies (STN 125742/0.51; received August 16, 2021)
- C4591009 Synoposis: A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States.
- C4591021 protocol: Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine
- C4591014 protocol: Pfizer-BioNTech COVID19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California

2 PRODUCT INFORMATION

2.1 Product Description

The Pfizer-BioNTech COVID-19 Vaccine COMIRNATY contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The product is a frozen suspension for intramuscular injection.

The product is administered as a series of two doses (0.3 mL) each 21 days apart by intramuscular injection.

2.2 Proposed Indication

The proposed indication for Pfizer-BioNTech COVID-19 Vaccine COMIRNATY in the United States is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

3 POST-AUTHORIZATION SAFETY AND EFFECTIVENESS STUDIES

In Response to CBER 28 July 2021 Information Request Regarding Post-marketing Safety Study(ies) (STN 125742/0.30; received August 3, 2021), the sponsor provided required number of cases to detect Myocarditis risk under

different assumptions of background rates. The sponsor also compared four post-authorization safety studies C4591009 (US), C4591011 (US), C4591012 (US), and C4591021(EU) to assess increased risk of safety events of interest, including myocarditis/pericarditis.

Reviewer comment: Among the four proposed post-authorization safety studies, two studies C4591009 (US) and C4591021(EU) have relatively large source population. The estimated number of individuals ≤30 years administered Pfizer vaccine is approximately 14.1 million in C4591009 and approximately 4.1 million in C4591021. It would be useful to include these two safety studies as postmarketing requirements (PMRs).

Please provide protocols for the C4591021 study and C4591021 substudy.

The sponsor submitted C4591009 protocol synopsis, and the protocol is expected to be finalized by August 31, 2021.

Below are the comments for C4591009 protocol synopsis:

1. *The primary analysis in the post-authorization safety study C4591009 protocol synopsis uses a concurrent unexposed cohort. People without vaccination codes could receive their COVID vaccinations outside of the system, and exposure misclassification could bias the results. The self-controlled methods such as self-controlled risk interval (SCRI) are less susceptible to bias due to exposure misclassification. SCRI with a post-vaccination control window was proposed as a sensitivity analysis.*

   Please clarify how you plan to assess the magnitude of exposure misclassification for the concurrent unexposed cohort and quantify the bias. If the magnitude of the exposure misclassification is large, please consider using the SCRI as the primary analysis. The proposed SCRI control window has the same length as the risk interval, which may decrease the risk of time-varying confounding bias but could result in more limited person time for some AESIs thus impacting the power of the SCRI analysis. Since SCRI allows the control window to have a different length than the risk window, please consider using a longer control window (e.g., multiples of the risk window) in the primary analysis, while maintaining the shorter control window for a sensitivity analysis. Please provide length of risk interval for each AESI.

2. *Table 1 on Page 5 of the Response to Information Request provided the required number of cases to detect myocarditis under different assumptions with a self-controlled case series (SCCS) analysis. The study C4591009 protocol synopsis proposed a SCRI analysis. SCCS samples cases only, SCRI samples vaccinated individuals only, and the control interval could differ between these two study designs even with the same length of risk interval. Please clarify the length and definition of control interval in the Table 1 sample size calculation. The choice of risk window is critical for SCRI. Because the onset of myocarditis was typically*

within several days after mRNA COVID-19 vaccination, please add a 7-day risk window to the SCRI analysis in addition to the proposed 14-day and 21-day risk window. Please also provide the sample size calculation for a 7-day risk window for myocarditis.

For study C4591009 protocol synopsis, the sample size calculation on Page 14 was based on a true RR=1. Please recalculate the sample size under alternative RRs.

In Response to CBER 10 August 2021 Information Request Regarding Post-marketing Safety Studies (STN 125742/0.42; received August 11, 2021), the sponsor addressed questions regarding study C4591009 and provided protocol for study C4591021.

Reviewer comment:

Below are the comments for sponsor's response regarding C4591009(US):

1. *The sponsor addressed exposure misclassification issue in the full C4591009 protocol (to be submitted by August 31, 2021) with pre-specified feasibility assessment. If vaccine coverage estimates differ meaningfully from the "benchmarking" estimates, the sponsor may consider the SCRI or the cohort design with historical unexposed comparators as the primary study designs and/or consider linkage to immunization registries if feasible.*

   The sponsor's response is acceptable.

   The COVID pandemic could have short-term and long-term impact on people's health seeking behavior. For historical unexposed comparators, please clarify how you plan to evaluate the temporal trend of time varying confounders.

   Page 12 of the C4591009 protocol synopsis mentioned ICD-9-CM and ICD-10-CM codes. ICD-10-CM was effective as of Oct 1, 2015. Please clarify whether historical unexposed comparators before Oct 1, 2015 will be used. There are differences between the ICD-9-CM and ICD-10-CM codes, and bias could be introduced. Please clarify how you plan to address the differences between the ICD-9-CM and ICD-10-CM system.

2. *The length of the control window in the SCRI analyses will be assessed separately for each outcome and the risk intervals for each safety event of interest will be provided in Section 9.3.2.1 of the full C4591009 protocol.*

   The sponsor's response is acceptable.

3. *The sponsor will incorporate a 7-day risk period for myocarditis into the protocols.*

   The sponsor's response is acceptable.