PHARMACOVIGILANCE PLAN FOR

BIOLOGIC LICENSE APPLICATION #125742

OF

COVID-19 mRNA vaccine (nucleoside modified) (BNT162b2, PF-07302048)

Date of Report: 28 JULY 2021

Version 1.1

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LIST OF ABBREVIATIONS

Abbreviation	Definition of Term
AE	adverse event
AESI	adverse event of special interest
A:G	albumin:globulin
ARDS	acute respiratory distress syndrome
BALB/c	bagg albino
BC	Brighton Collaboration
BEST	biologics effectiveness and safety
BLA	biologics license application
BMI	body mass index
BP	blood pressure
CD4, CD8	cluster of differentiation-4, 8
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CSR	clinical study report
CT	clinical trial
DART	developmental and reproductive toxicology
DCA	data capture aid
DLP	data-lock point
DoD	Department of Defense
ECDC	European Center for Disease Control
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EU	European Union
EUA	emergency use authorization
FDA	(US) Food and Drug Administration
GLP	good laboratory practice
HbA1c	glycated hemoglobin
HBV	hepatitis b virus
HCV	hepatitis c virus
HIV	human immunodeficiency virus
IA	interim analysis
ICU	intensive care unit
IFN	interferon
IL-4	interleukin-4
IM	intramuscular(ly)
IMD	index of multiple deprivation
IND	investigational new drug
LNP	lipid nanoparticle
MAA	marketing authorization applicant
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition of Term
MERS-CoV	Middle East respiratory syndrome–coronavirus
MHS	Military Health System
MIS-C	multisystem inflammatory syndrome in children
MOA	mechanism of action
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	messenger ribonucleic acid
NDA	new drug application
NHP	nonhuman primate
NICE	National Institute for Health and Care Excellence
OCS	oral corticosteroids
PK	pharmacokinetic
PT	Preferred Term
PVP	pharmacovigilance plan
RBC	red blood cell
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
siRNA	small-interfering RNA
SMQ	standardised MedDRA query
Tdap	tetanus, diphtheria, and acellular pertussis
TESSy	The European Surveillance System
Th1	T helper cell type 1
Th2	T helper cell type 2
UK	United Kingdom
US	United States
USP	United States pharmacopeia
V8	variant 8
V9	variant 9
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
WBC	white blood cells
WHO	World Health Organization
WOCBP	women of childbearing potential

1. INTRODUCTION

1.1. Product Details

Table 1. Product Details[a]

Product	COVID-19 mRNA Vaccine (nucleoside modified), herein after referred to as BNT162b2 is a nucleoside-modified messenger RNA –(modRNA) encoding the viral spike (S) glycoprotein of severe acute respiratory syndrome coronavirus (SARS-CoV-2).
Brief description of the product	Chemical class: Nucleoside-modRNA formulated in lipid particles. Mechanism of Action: The modRNA in the BNT162b2 is formulated in lipid particles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19. Important information about its composition: • The BNT162b2 is supplied as a frozen suspension in multiple dose vials. • Each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. • Each dose of the BNT162b2 contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2. • Each dose of the BNT162b2 also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose. • The BNT162b2 does not contain preservative. • The vial stoppers are not made with natural rubber latex.
Indication	Proposed: Active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.
Dosage and route of administration	Proposed: Series of two doses (0.3 mL each) 3 weeks apart, intramuscularly.

a. COVID-19 mRNA vaccine (nucleoside-modified) US Prescribing Information

Data Lock Point / Data cut-off:	16 years and older	13 March 2021 (Pfizer Clinical Database)
		23 October 2020 (BioNTech Clinical Database)
		28 February 2021 (Pfizer Safety Database)
	12 to 15 years older	13 March 2021 (Pfizer Clinical Database)
		28 February 2021 (Pfizer Safety Database)
	Important Identified Risk "Myocarditis and pericarditis"	18 June 2021 (Pfizer Safety Database)

2. SAFETY SPECIFICATION

2.1. Elements of the Safety Specification

2.1.1. Non-Clinical

Nonclinical evaluation of BNT162b2 included pharmacology (mouse immunogenicity and NHP immunogenicity and challenge studies), pharmacokinetic (series of biodistribution, metabolism and pharmacokinetic studies), and toxicity (2 GLP rat repeat-dose toxicity and a GLP DART) studies in vitro and in vivo. No additional toxicity studies are planned for BNT162b2.

Nonclinical studies in mice and NHP for BNT162b2 demonstrated both a strong neutralizing antibody response and a Th1-type $CD4^+$ and an $IFN\gamma^+$ $CD8^+$ T-cell response. The Th1 profile is characterized by a strong IFNγ, but not IL-4, response indicating the absence of a potentially deleterious Th2 immune response and is a pattern favored for vaccine safety and efficacy.[1] Rhesus macaques (Study VR-VRT-10671) that had received two IM immunizations with 100 µg BNT162b2 or saline 21 days apart were challenged with 1.05×10^6 plaque forming units of SARS-CoV-2 (strain USA-WA1/2020), split equally between the intranasal and intratracheal routes.[2] BNT162b2 provided complete protection from the presence of detectable viral RNA in the lungs compared to the saline control with no clinical, radiological or histopathological evidence of vaccine-elicited disease enhancement.

An intravenous rat PK study, using an LNP with the identical lipid composition asBNT162b2, demonstrated that the novel lipid excipients in the LNP formulation, ALC-0315 and ALC-0159, distribute from the plasma to the liver. While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in feces was ~1% for ALC-0315 and ~50% for ALC-0159. Further studies indicated metabolism played a role in the elimination of ALC-0315. Biodistribution was assessed using luciferase expression as a surrogate reporter formulated likeBNT162b2, with the identical lipid composition. After IM injection of the LNP-formulated RNA encoding luciferase in BALB/c mice, luciferase protein expression was demonstrated at the site of injection 6 hours post dose and expression decreased over time to almost reach background levels after 9 days. Luciferase was detected to a lesser extent in the liver; expression was present at 6 hours after injection and was not detected by 48 hours after injection. After IM administration of a radiolabeled LNP-mRNA formulation containing ALC-0315 and ALC-0159 to rats, the percent of administered dose was also greatest at the injection site. Outside of the injection site, total recovery of radioactivity was greatest in the liver and much lower in the spleen, with very little recovery in the adrenal glands and ovaries. The metabolism of ALC-0315 and ALC-0159 was evaluated in blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys, and humans. The in vivo metabolism was examined in rat plasma, urine, feces, and liver samples from the PK study. ALC-0315 and ALC-0159 are metabolized by hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

In GLP toxicity studies, two variants of the BNT162b2 candidate were tested, designated "variant 8" and "variant 9" (V8 and V9, respectively). The variants differ only in their codon optimization sequences which are designed to improve antigen expression, otherwise the

amino acid sequences of the encoded antigens are identical. BNT162b2 (V9) was evaluated clinically and submitted for application. Two GLP-compliant repeat-dose toxicity studies were performed in Wistar Han rats; one with each variant. Both studies were 17 days in duration with a 3-week recovery period. A GLP-compliant DART study in Wistar Han rats has also been completed. Safety pharmacology, genotoxicity and carcinogenicity studies have not been conducted, in accordance with the 2005 WHO vaccine guideline.[3]

The IM route of exposure was selected for nonclinical investigations as it is the clinical route of administration. Rats were selected as the toxicology test species as they demonstrated an antigen-specific immune response to the vaccine and are routinely used for regulatory toxicity studies with an extensive historical safety database.

Administration of up to 100 µg BNT162b2 by IM injection to male and female Wistar Han rats once every week, for a total of 3 doses, was tolerated without evidence of systemic toxicity. Expected inflammatory responses to the vaccine were evident such as edema and erythema at the injection sites, transient elevation in body temperature, elevations in WBC count and acute phase reactants, and lower A:G ratios. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunizations. Changes secondary to inflammation included slight and transient reduction in body weights and transient reduction in reticulocytes, platelets and RBC mass parameters. Decreased reticulocytes were reported in rats treated with the licensed LNP-siRNA pharmaceutical Onpattro™ (NDA # 210922) but have not been observed in humans treated with this biotherapeutic[4] suggesting this is a species-specific effect. Decreased platelet counts were noted after repeat administration, but were small in magnitude of change, likely related to inflammation-related platelet activation and consumption, and unassociated with other alterations in hemostasis. Elevated levels of gamma-glutamyl transferase were observed in the first repeat-dose toxicity study with BNT162b2 (V8) without evidence of cholestasis or hepatobiliary injury but was not recapitulated in the second repeat dose-toxicity study with BNT162b2 (V9), the final clinical candidate. All changes in clinical pathology parameters and acute phase proteins were reversed at the end of the recovery phase for BNT162b2, with the exception of low magnitude higher red cell distribution width (consistent with a regenerative erythroid response) and lower A:G ratios (resulting from acute phase response) in animals administered BNT162b2. Macroscopic pathology and organ weight changes were also consistent with immune activation and inflammatory response and included increased size and/or weight of draining iliac lymph nodes and spleen. Vaccine-related microscopic findings at the end of the dosing phase consisted of edema and inflammation in injection sites and surrounding tissues, increased cellularity in the draining iliac lymph nodes, bone marrow and spleen and hepatocyte vacuolation in the liver. Vacuolation of periportal hepatocytes, the only test article-related liver microscopic finding, was not associated with any microscopic evidence of hepatic injury or hepatic functional effects (i.e., liver functional enzymes were not elevated) and may be associated with hepatocyte uptake of the LNP lipids.[5] Microscopic findings at the end of the dosing phase were partially or completely recovered in all animals at the end of the 3-week recovery period for BNT162b2. A robust immune response was elicited to the BNT162b2 antigen.

Administration of BNT162b2 to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg) was associated with non-adverse effects (body

weight, food consumption and effects localized to the injection site) after each dose administration. However, there were no effects of BNT162b2 administration on mating performance, fertility, or any ovarian or uterine parameters in the F0 female rats nor on embryo-fetal or postnatal survival, growth, or development in the F1 offspring. An immune response was confirmed in F0 female rats following administration of each vaccine candidate and these responses were also detectable in the F1 offspring (fetuses and pups).

In summary, the nonclinical safety findings related to BNT162b2 administration primarily represent an expected immune reaction to vaccine administration and are clinically manageable or acceptable risks in the intended population. The key safety findings regarding BNT162b2 from nonclinical studies and their relevance to human usage are presented in Table 2. There was no evidence of vaccine-elicited disease enhancement.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Nonclinical Studies[a]	Relevance to Human Usage
Pharmacology	
NHP Challenge Model • No evidence of vaccine-elicited disease enhancement.	• Suggests low risk of vaccine-enhanced disease in humans; being investigated in CTs.
Toxicity	
Injection site reactions: • Injection site reactions were common and reversible or showed signs of reversibility at the end of the 3-week recovery period in nonclinical studies.	• In common with other vaccines, BNT162b2 administration has the potential to generate injection site reactions such as edema and erythema at the injection sites.
Inflammation and immune activation: • Evidence of inflammation or immune activation was common, reversible, and included transiently higher body temperature, higher circulating WBCs, and higher acute phase reactants. Secondarily, transiently lower body weights, reticulocytes, platelets, and RBC mass parameters were observed.	• In common with all vaccines, BNT162b2 administration has the potential to generate inflammation which can lead to increased body temperature, higher circulating WBCs and higher acute phase proteins. • Decreased reticulocytes have not been observed in humans treated with the LNP-siRNA pharmaceutical Onpattro[4], suggesting this finding in rats is a species-specific effect. • BNT162b2 administration has the potential to transiently decrease platelets and RBC mass parameters. These slight decreases are not likely to be clinically meaningful due to their small magnitude.
Developmental and Reproductive Toxicity • No vaccine-related effects on female fertility or the development of fetuses or offspring were observed in a DART study of BNT162b2 in rats.	• No effects are anticipated in WOCBP, pregnant women or their offspring.

a. Safety pharmacology, genotoxicity, and carcinogenicity studies were not conducted, in accordance with 2005 WHO vaccine guideline, as they are generally not considered necessary to support development and licensure of vaccines for infectious diseases.[3] In addition, the components of the vaccine construct are lipids and RNA and are not expected to have carcinogenic or genotoxic potential.

2.1.2. Clinical

2.1.2.a. Limitations of the Human Safety Database

The pivotal study was initially planned to enroll approximately 30,000 participants, which would have a probability of 78% of detecting an AE with a frequency of 0.01% (1/1000) and a probability of 95% of detecting an AE with a frequency of 0.02% (1/500). The protocol was amended to enroll approximately 46,000 participants, which would slightly enhance the ability to detect AEs. However, rarer events might not be detected.

Participants in the pivotal study were initially planned to be followed for up to 24 months in order to assess the potential for late-occurring adverse reactions, such as the theoretical risk of VAED. After completing the final efficacy analysis with vaccine efficacy shown to be 95%, and obtaining regulatory authorization to vaccinate in many countries, Pfizer-BioNTech started to unblind all participants to determine those randomized to placebo so that they could be offered vaccine in accordance with local authorization. To date, most placebo subjects have been unblinded to receive active vaccine at or prior to 6 months after the second dose, therefore, a placebo group for comparison of safety data is only available for up to 6 months post Dose 2.

2.1.2.a.1. Clinical Trial Exposure

Brief Overview of Development

BioNTech is conducting a first-in-human dose level–finding Phase 1/2 study (BNT162-01) in Germany to gather safety and immunogenicity data to enable evaluation of 4 vaccines candidates individually to inform the overall clinical development of a BNT162b2.

BNT162-01 is not conducted under the US IND application but is being conducted under a German Clinical Trial Application.

Four vaccine candidates were evaluated in Study BNT162-01. Based on safety and immunogenicity results from this study, 2 vaccine candidates, BNT162b1 and BNT162b2, were selected for evaluation in Study C4591001, which is a Phase 1/2/3 randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in healthy adults (conducted under IND 019736).

Phase 1 of Study C4591001 comprised dose-level–finding evaluations of the 2 selected vaccine candidates; multiple dose levels (some corresponding to those evaluated in Study BNT162-01) were evaluated. Study vaccine was administered using the same 2-dose schedule as in Study BNT162-01 (21 days apart). Dose levels were administered first to an 18- to 55-year age cohort, then to a 65- to 85-year age cohort.

Both vaccine candidate constructs were safe and well tolerated. BNT162b2 at the 30-µg dose level was selected and advanced to the Phase 2/3 expanded cohort and efficacy evaluation primarily because:

- the reactogenicity profile for BNT162b2 was more favorable than BNT162b1 in both younger and older adults with similar immunogenicity results;
- in the NHP challenge study (VR-VTR-10671, see Section 2.1.1), a trend toward earlier clearance of BNT162b2 was observed in the nose.

Phase 2 of the study (for which enrollment has completed) comprised the evaluation of safety and immunogenicity data for the first 360 participants (180 from the active vaccine group and 180 from the placebo group, with each group divided between the younger and older age cohorts) entering the study after completion of Phase 1.

The Phase 3 part of the study (which is ongoing) evaluates the efficacy and safety in all participants (including the first 360 participants from Phase 2). Phase 3 introduced:

- enrollment of participants 16 to 17 years of age to be evaluated with the 18- to 55-year-old cohort,
- enrollment of a 12- to 15-year-old cohort,
- immunogenicity data from the 12- to 15-year-old cohort (Table 3, Table 5, Table 11, Table 13, Table 15, and Table 17),anticipated to bridge to the 16- to 25-year-old cohort.

Participants in the pivotal study were initially planned to be followed for up to 24 months in order to assess the potential for late-occurring adverse reactions, such as the theoretical risk of VAED including VAERD. After completing the final efficacy analysis with vaccine efficacy shown to be 95%, and obtaining regulatory authorisation to vaccinate in many countries, Pfizer-BioNTech started to unblind all participants to determine those participants randomised to placebo so that they could be offered vaccine in accordance with local authorisation. To date, most placebo subjects have been unblinded to receive active vaccine at or prior to 6 months after the second dose, therefore, a placebo group for comparison of safety data is only available for up to 6 months post Dose 2.

The initial efficacy analysis on the 16 years and older population was event-driven, with prespecified interim analyses after accrual of at least 62, 92, and 120 cases and a final analysis at 164 cases.

A further efficacy analysis has been conducted on 12- to ≤15-year-old cohort participants and on 16 years and older participants cohort participants reported by 13 March 2021.

Ongoing BNT162b2 studies at the cut-off of the clinical database (13 March 2021) also include:

- C4591005: *A phase 1/2 study to evaluate the safety, tolerability, and immunogenicity of an RNA vaccine candidate against COVID-19 in healthy Japanese adults.*
  One hundred sixty participants were randomly assigned in a 3:1 ratio to study intervention (candidate vaccine: 120, placebo: 40).

- C4591015: *A phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older.*
  Approximately 4000 pregnant women at 24 to 34 weeks gestation are being randomized in a 1:1 ratio to vaccine or placebo.

- C4591017: *A phase 3 study to evaluate the safety, tolerability, and immunogenicity of multiple production lots and dose levels of BNT162b2 against COVID-19 in healthy participants.*
  Approximately 340 participants were randomly assigned to each of 3 US lots and to a 20-µg arm and approximately 170 participants were randomly assigned an EU lot, for a total of approximately 1530 randomized participants in 5 study arms.

Clinical Trial Exposure

Population for analysis of CTs data in this US Pharmacovigilance Plan includes the following 2 studies:

- 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 RNA vaccine candidates against COVID-19 in healthy individuals*.

- BNT162-01: *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 adults.*

Participants 16 years of age and older

At the cut-off date of 13 March 2021, a total of 46,505 participants were vaccinated in the BNT162b2 clinical development program:

- 21,745 participants received 2 doses and 360 received 1 dose of BNT162b2 during the blinded follow-up period; 96 participants from study BNT162-01 received 2 doses of the vaccine.

- 19,647 participants, who originally received placebo, then received 1 dose of BNT162b2 in the Open-Label Follow-up period after unblinding. (none from study BNT162-01).

Exposure to BNT162b2 for participants aged 16 years and older in the 2 ongoing studies by number of doses, and demographic characteristics is shown in Table 3 through Table 21.

In addition, exposure in clinical studies in special populations is provided in Table 22 and Table 23.

Participants 12 to 15 years of age

At the cut-off date of 13 March 2021, a total of 2260 participants were vaccinated in the BNT162b2 clinical development program:

Clinical study exposure data for the 12- to 15 years of age are provided for the ongoing study C4591001 at the cut-off date of 13 March 2021.

In this study

- 1124 participants received 2 doses and 7 received 1 dose of BNT162b2 in the Blinded-Placebo Controlled Follow-up period.

- 49 participants who originally received placebo, then received 1 dose of BNT162b2 in the Open-Label Follow-up period after unblinding.

Exposure to BNT162b2 for participants aged 12- to 15 years of age by number of doses and demographic characteristics is shown in Table 3,Table 5, Table 11, Table 13, Table 15, Table 17. In addition, exposure in clinical studies in special populations is provided in Table 22 and Table 23.

Table 3. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥12 years to ≤15 years		
Vaccine 30 µg		
1 Dose	7	7
2 Doses	1124	2248
Total	1131	2255
≥16 years to ≤17 years		
Vaccine 30 µg		
1 Dose	4	4
2 Doses	374	748
Total	378	752
≥18 years to ≤55 years		
Vaccine 10 µg		
2 Doses	12	24
Total	12	24
Vaccine 20 µg		
2 Doses	12	24
Total	12	24
Vaccine 30 µg		
1 Dose	267	267
2 Doses	12438	24876
Total	12705	25143
>55 years to ≤64 years		
Vaccine 30 µg		
1 Dose	67	67
2 Doses	4341	8682
Total	4408	8749
≥65 years to ≤74 years		
Vaccine 10 µg		
2 Doses	12	24
Total	12	24
Vaccine 20 µg		
2 Doses	9	18
Total	9	18
Vaccine 30 µg		
1 Dose	17	17
2 Doses	3624	7248
Total	3641	7265
≥75 years to ≤84 years		

Table 3. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 20 µg		
2 Doses	3	6
Total	3	6
Vaccine 30 µg		
1 Dose	3	3
2 Doses	899	1798
Total	902	1801
≥85 years		
Vaccine 30 µg		
1 Dose	2	2
2 Doses	21	42
Total	23	44

Note: 30 µg includes data from phase 1 and phase 2/3.
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s912

Table 4. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥16 years to ≤17 years		
Vaccine 30 µg		
1 Dose	3	3
≥18 years to ≤55 years		
Vaccine 30 µg		
1 Dose	58	58
>55 years to ≤64 years		
Vaccine 30 µg		
1 Dose	17	17
≥65 years to ≤74 years		
Vaccine 30 µg		
1 Dose	8	8
≥75 years to ≤84 years		
Vaccine 30 µg		
1 Dose	1	1

Table 4. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥85 years		
Vaccine 30 µg		
1 Dose	2	2

Note: 30 µg includes data from phase 1 and phase 2/3.
Note: Subjects who received 2nd Dose of BNT162b2 after unblinding.
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Table 5. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥12 years to ≤15 years[a]		
Vaccine 30 µg		
1 Dose	30	30
2 Doses	19	38
Total	49	68
≥16 years to ≤17 years		
Vaccine 30 µg		
1 Dose	107	107
2 Doses	186	372
Total	293	479
≥18 years to ≤55 years		
Vaccine 30 µg		
1 Dose	2713	2713
2 Doses	8419	16838
Total	11132	19551
>55 years to ≤64 years		
Vaccine 30 µg		
1 Dose	655	655
2 Doses	3330	6660
Total	3985	7315
≥65 years to ≤74 years		
Vaccine 30 µg		

Table 5. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
1 Dose	128	128
2 Doses	3286	6572
Total	3414	6700
≥75 years to ≤84 years		
Vaccine 30 µg		
1 Dose	23	23
2 Doses	783	1566
Total	806	1589
≥85 years		
Vaccine 30 µg		
1 Dose	1	1
2 Doses	16	32
Total	17	33

Note: 30 µg includes data from phase 1 and phase 2/3.
a. Includes subjects who became eligible for unblinding at 16 years of age, confirmed to have received placebo originally and then received BNT162b2 post unblinding.
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:
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Table 6. Exposure to BNT162b2 by Age Group and Dose (BNT162-01)

Age Group Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
≥18 years to ≤64 years		
Vaccine 1 µg		
1 Dose	1	1
2 Doses	11	22
Total	12	23
Vaccine 3 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24

Table 6. Exposure to BNT162b2 by Age Group and Dose (BNT162-01)

Age Group Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 10 µg		
1 Dose	1	1
2 Doses	11	22
Total	12	23
Vaccine 20 µg		
1 Dose	0	0
2 Doses	17	34
Total	17	34
Vaccine 30 µg		
1 Dose	0	0
2 Doses	18	36
Total	18	36
≥65 years to ≤74 years		
Vaccine 1 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 3 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 10 µg		
1 Dose	0	0
2 Doses	5	10
Total	5	10
Vaccine 20 µg		
1 Dose	0	0

Table 6. Exposure to BNT162b2 by Age Group and Dose (BNT162-01)

Age Group Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
2 Doses	6	12
Total	6	12
Vaccine 30 µg		
1 Dose	0	0
2 Doses	6	12
Total	6	12
≥75 years to ≤84 years		
Vaccine 1 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 3 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 10 µg		
1 Dose	0	0
2 Doses	1	2
Total	1	2
Vaccine 20 µg		
1 Dose	0	0
2 Doses	1	2
Total	1	2
Vaccine 30 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0

PFIZER CONFIDENTIAL SDTM Creation: 24NOV2020 (15:06) Source Data: adsl Table Generation: 10MAR2021 (11:32) (Cutoff date:23OCT2020, Snapshot Date: 23OCT2020)
Output File: ex_b2_age_dose2 rtf

Table 7. Exposure to BNT162b2 by Dose (Totals) (C4591001) – Blinded Placebo-Controlled Follow-up Period

Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 10 µg		
2 Doses	24	48
Total	24	48
Vaccine 20 µg		
2 Doses	24	48
Total	24	48
Vaccine 30 µg		
1 Dose	367	367
2 Doses	22821	45642
Total	23188	46009

Note: 30 µg includes data from phase 1 and phase 2/3.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s922

Table 8. Exposure to BNT162b2 by Dose (Totals) (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg		
1 Dose	89	89

Note: 30 µg includes data from phase 1 and phase 2/3.
Note: Subjects who received 2nd Dose of BNT162b2 after unblinding.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2 unblinded/C4591001 PVP BLA/adsl s9223

Table 9. Exposure to BNT162b2 by Dose (Totals) (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg		
1 Dose	3657	3657
2 Doses	16039	32078
Total	19696	35735

Table 9. Exposure to BNT162b2 by Dose (Totals) (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses

Note: 30 µg includes data from phase 1 and phase 2/3.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2 unblinded/C4591001 PVP BLA/adsl s9222

Table 10. Exposure to BNT162b2 by Dose (Totals) (BNT162-01)

Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 1 µg		
1 Dose	1	1
2 Doses	11	22
Total	12	23
Vaccine 3 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24
Vaccine 10 µg		
1 Dose	1	1
2 Doses	23	46
Total	24	47
Vaccine 20 µg		
1 Dose	0	0
2 Doses	24	48
Total	24	48
Vaccine 30 µg		
1 Dose	0	0
2 Doses	24	48
Total	24	48

PFIZER CONFIDENTIAL SDTM Creation: 24NOV2020 (15:06) Source Data: adsl Table Generation: 10MAR2021 (11:49) (Cutoff date:23OCT2020, Snapshot Date: 23OCT2020)
Output File: ex_b2_dose.rtf

Table 11. Exposure to BNT162b2 by Dose, Age Group, and Gender (C4591001) – Blinded Placebo-Controlled Follow-up Period

Dose Age Group	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses	
	Male	Female	Male	Female
Vaccine 10 µg				
≥18 years to ≤55 years	5	7	10	14
≥65 years to ≤74 years	2	10	4	20
Total	7	17	14	34
Vaccine 20 µg				
≥18 years to ≤55 years	6	6	12	12
≥65 years to ≤74 years	4	5	8	10
≥75 years to ≤84 years	1	2	2	4
Total	11	13	22	26
Vaccine 30 µg				
≥12 years to ≤15 years	567	564	1128	1127
≥16 years to ≤17 years	187	191	373	379
≥18 years to ≤55 years	6456	6249	12770	12373
>55 years to ≤64 years	2231	2177	4421	4328
≥65 years to ≤74 years	1934	1707	3858	3407
≥75 years to ≤84 years	511	391	1020	781
≥85 years	12	11	23	21
Total	11898	11290	23593	22416

Note: 30 µg includes data from phase 1 and phase 2/3.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s932

Table 12. Exposure to BNT162b2 by Dose, Age Group, and Gender (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

Dose Age Group	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses	
	Male	Female	Male	Female
Vaccine 30 µg				
≥16 years to ≤17 years	0	3	0	3
≥18 years to ≤55 years	24	34	24	34
>55 years to ≤64 years	12	5	12	5
≥65 years to ≤74 years	4	4	4	4

Table 12. Exposure to BNT162b2 by Dose, Age Group, and Gender (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses	
Dose Age Group	**Male**	**Female**	**Male**	**Female**
≥75 years to ≤84 years	0	1	0	1
≥85 years	1	1	1	1
Total	41	48	41	48

Note: 30 µg includes data from phase 1 and phase 2/3.
Note: Subjects who received 2nd Dose of BNT162b2 after unblinding.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s9323

Table 13. Exposure to BNT162b2 by Dose, Age Group, and Gender (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses	
Dose Age Group	**Male**	**Female**	**Male**	**Female**
Vaccine 30 µg				
≥12 years to ≤15 years[a]	26	23	36	32
≥16 years to ≤17 years	152	141	250	229
≥18 years to ≤55 years	5424	5708	9450	10101
>55 years to ≤64 years	1973	2012	3602	3713
≥65 years to ≤74 years	1801	1613	3530	3170
≥75 years to ≤84 years	495	311	976	613
≥85 years	13	4	25	8
Total	9884	9812	17869	17866

Note: 30 µg includes data from phase 1 and phase 2/3.
a. Includes subjects who became eligible for unblinding at 16 years of age, confirmed to have received placebo originally and then received BNT162b2 post unblinding.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s932_open

Table 14. Exposure to BNT162b2 by Dose, Age Group, and Gender (BNT162-01)

	No. of Subjects Exposed to BNT162b2		Total No. of Vaccine Doses	
Dose Age Group	**Male**	**Female**	**Male**	**Female**
Vaccine 1 µg				
≥18 years to ≤64 years	7	5	14	9
≥65 years to ≤74 years	0	0	0	0
≥75 years to ≤84 years	0	0	0	0
Total	7	5	14	9
Vaccine 3 µg				
≥18 years to ≤64 years	5	7	10	14
≥65 years to ≤74 years	0	0	0	0
≥75 years to ≤84 years	0	0	0	0
Total	5	7	10	14
Vaccine 10 µg				
≥18 years to ≤64 years	8	10	16	19
≥65 years to ≤74 years	3	2	6	4
≥75 years to ≤84 years	1	0	2	0
Total	12	12	24	23
Vaccine 20 µg				
≥18 years to ≤64 years	7	10	14	20
≥65 years to ≤74 years	1	5	2	10
≥75 years to ≤84 years	0	1	0	2
Total	8	16	16	32
Vaccine 30 µg				
≥18 years to ≤64 years	10	8	20	16
≥65 years to ≤74 years	2	4	4	8
≥75 years to ≤84 years	0	0	0	0
Total	12	12	24	24

PFIZER CONFIDENTIAL SDTM Creation: 24NOV2020 (15:06) Source Data: adsl Table Generation: 10MAR2021 (11:53) (Cutoff date:23OCT2020, Snapshot Date: 23OCT2020)
Output File: ex_b2_age_dose_sex rtf

Table 15. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥12 years to ≤15 years		
Vaccine 30 µg		
Racial origin		
White	971	1937
Black or African American	52	103
Asian	72	143
American Indian or Alaska Native	4	8
Native Hawaiian or other Pacific Islander	3	6
Multiracial	23	46
Not reported	6	12
Total	1131	2255
Ethnic origin		
Hispanic/Latino	132	263
Non-Hispanic/non-Latino	997	1988
Not reported	2	4
Total	1131	2255
≥16 years to ≤17 years		
Vaccine 30 µg		
Racial origin		
White	309	614
Black or African American	30	60
Asian	22	44
American Indian or Alaska Native	4	8
Native Hawaiian or other Pacific Islander	3	6
Multiracial	10	20
Total	378	752
Ethnic origin		
Hispanic/Latino	49	98
Non-Hispanic/non-Latino	329	654
Total	378	752
≥18 years to ≤55 years		
Vaccine 10 µg		
Racial origin		
White	11	22
Asian	1	2
Total	12	24
Ethnic origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	11	22

Table 15. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Total	12	24
Vaccine 20 µg		
Racial origin		
White	10	20
Black or African American	2	4
Total	12	24
Ethnic origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	11	22
Total	12	24
Vaccine 30 µg		
Racial origin		
White	9923	19637
Black or African American	1400	2764
Asian	683	1358
American Indian or Alaska Native	161	311
Native Hawaiian or other Pacific Islander	40	80
Multiracial	427	851
Not reported	71	142
Total	12705	25143
Ethnic origin		
Hispanic/Latino	4000	7874
Non-Hispanic/non-Latino	8650	17160
Not reported	55	109
Total	12705	25143
>55 years to ≤64 years		
Vaccine 30 µg		
Racial origin		
White	3719	7388
Black or African American	430	849
Asian	135	267
American Indian or Alaska Native	30	58
Native Hawaiian or other Pacific Islander	8	15
Multiracial	76	152
Not reported	10	20
Total	4408	8749
Ethnic origin		
Hispanic/Latino	965	1903
Non-Hispanic/non-Latino	3413	6786

Table 15. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Not reported	30	60
Total	4408	8749
≥65 years to ≤74 years		
Vaccine 10 µg		
Racial origin		
White	12	24
Total	12	24
Ethnic origin		
Non-Hispanic/non-Latino	12	24
Total	12	24
Vaccine 20 µg		
Racial origin		
White	9	18
Total	9	18
Ethnic origin		
Non-Hispanic/non-Latino	9	18
Total	9	18
Vaccine 30 µg		
Racial origin		
White	3272	6528
Black or African American	219	437
Asian	82	164
American Indian or Alaska Native	22	44
Native Hawaiian or other Pacific Islander	6	12
Multiracial	30	60
Not reported	10	20
Total	3641	7265
Ethnic origin		
Hispanic/Latino	583	1158
Non-Hispanic/non-Latino	3038	6067
Not reported	20	40
Total	3641	7265
≥75 years to ≤84 years		
Vaccine 20 µg		
Racial origin		
White	3	6
Total	3	6
Ethnic origin		
Non-Hispanic/non-Latino	3	6

Table 15. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Total	3	6
Vaccine 30 µg		
Racial origin		
White	838	1673
Black or African American	22	44
Asian	31	62
American Indian or Alaska Native	3	6
Native Hawaiian or other Pacific Islander	1	2
Multiracial	7	14
Total	902	1801
Ethnic origin		
Hispanic/Latino	107	213
Non-Hispanic/non-Latino	789	1576
Not reported	6	12
Total	902	1801
≥85 years		
Vaccine 30 µg		
Racial origin		
White	20	38
Asian	1	2
American Indian or Alaska Native	1	2
Multiracial	1	2
Total	23	44
Ethnic origin		
Hispanic/Latino	2	4
Non-Hispanic/non-Latino	21	40
Total	23	44

Note: 30 µg includes data from phase 1 and phase 2/3.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s942

Table 16. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥16 years to ≤17 years		
Vaccine 30 µg		
Racial origin		
White	3	3
Total	3	3
Ethnic origin		
Non-Hispanic/non-Latino	3	3
Total	3	3
≥18 years to ≤55 years		
Vaccine 30 µg		
Racial origin		
White	46	46
Black or African American	2	2
Asian	2	2
American Indian or Alaska Native	8	8
Total	58	58
Ethnic origin		
Hispanic/Latino	31	31
Non-Hispanic/non-Latino	27	27
Total	58	58
>55 years to ≤64 years		
Vaccine 30 µg		
Racial origin		
White	14	14
Asian	1	1
American Indian or Alaska Native	2	2
Total	17	17
Ethnic origin		
Hispanic/Latino	10	10
Non-Hispanic/non-Latino	7	7
Total	17	17
≥65 years to ≤74 years		
Vaccine 30 µg		
Racial origin		
White	8	8
Total	8	8
Ethnic origin		
Hispanic/Latino	5	5

Table 16. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Non-Hispanic/non-Latino	3	3
Total	8	8
≥75 years to ≤84 years		
Vaccine 30 µg		
Racial origin		
White	1	1
Total	1	1
Ethnic origin		
Non-Hispanic/non-Latino	1	1
Total	1	1
≥85 years		
Vaccine 30 µg		
Racial origin		
White	2	2
Total	2	2
Ethnic origin		
Non-Hispanic/non-Latino	2	2
Total	2	2

Note: 30 µg includes data from phase 1 and phase 2/3.
Note: Subjects who received 2nd Dose of BNT162b2 after unblinding.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s9423

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥12 years to ≤15 years[a]		
Vaccine 30 µg		
Racial origin		
White	45	62
Asian	3	5
Multiracial	1	1
Total	49	68

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Ethnic origin		
Hispanic/Latino	2	4
Non-Hispanic/non-Latino	47	64
Total	49	68
≥16 years to ≤17 years		
Vaccine 30 µg		
Racial origin		
White	251	410
Black or African American	11	19
Asian	14	25
American Indian or Alaska Native	2	4
Native Hawaiian or other Pacific Islander	1	2
Multiracial	12	16
Not reported	2	3
Total	293	479
Ethnic origin		
Hispanic/Latino	26	43
Non-Hispanic/non-Latino	266	434
Not reported	1	2
Total	293	479
≥18 years to ≤55 years		
Vaccine 30 µg		
Racial origin		
White	8806	15340
Black or African American	1087	1899
Asian	619	1136
American Indian or Alaska Native	128	236
Native Hawaiian or other Pacific Islander	17	32
Multiracial	405	781
Not reported	70	127
Total	11132	19551
Ethnic origin		
Hispanic/Latino	3441	5300
Non-Hispanic/non-Latino	7635	14157
Not reported	56	94
Total	11132	19551
>55 years to ≤64 years		
Vaccine 30 µg		

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Racial origin		
White	3416	6271
Black or African American	331	592
Asian	120	227
American Indian or Alaska Native	35	67
Native Hawaiian or other Pacific Islander	4	7
Multiracial	63	120
Not reported	16	31
Total	3985	7315
Ethnic origin		
Hispanic/Latino	901	1560
Non-Hispanic/non-Latino	3067	5724
Not reported	17	31
Total	3985	7315
≥65 years to ≤74 years		
Vaccine 30 µg		
Racial origin		
White	3093	6076
Black or African American	187	360
Asian	78	154
American Indian or Alaska Native	20	39
Native Hawaiian or other Pacific Islander	6	12
Multiracial	22	43
Not reported	8	16
Total	3414	6700
Ethnic origin		
Hispanic/Latino	547	1060
Non-Hispanic/non-Latino	2842	5590
Not reported	25	50
Total	3414	6700
≥75 years to ≤84 years		
Vaccine 30 µg		
Racial origin		
White	752	1483
Black or African American	22	42
Asian	17	34
American Indian or Alaska Native	4	8
Multiracial	6	12
Not reported	5	10

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Total	806	1589
Ethnic origin		
Hispanic/Latino	89	174
Non-Hispanic/non-Latino	706	1393
Not reported	11	22
Total	806	1589
≥85 years		
Vaccine 30 µg		
Racial origin		
White	15	29
Asian	1	2
Multiracial	1	2
Total	17	33
Ethnic origin		
Non-Hispanic/non-Latino	17	33
Total	17	33

Note: 30 µg includes data from phase 1 and phase 2/3.
a. Includes subjects who became eligible for unblinding at 16 years of age, confirmed to have received placebo originally and then received BNT162b2 post unblinding.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s942_open

Table 18. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 10 µg		
Racial origin		
White	23	46
Asian	1	2
Total	24	48
Ethnic origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	23	46
Total	24	48
Vaccine 20 µg		

Table 18. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Racial origin		
White	22	44
Black or African American	2	4
Total	24	48
Ethnic origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	23	46
Total	24	48
Vaccine 30 µg		
Racial origin		
White	19052	37815
Black or African American	2153	4257
Asian	1026	2040
American Indian or Alaska Native	225	437
Native Hawaiian or other Pacific Islander	61	121
Multiracial	574	1145
Not reported	97	194
Total	23188	46009
Ethnic origin		
Hispanic/Latino	5838	11513
Non-Hispanic/non-Latino	17237	34271
Not reported	113	225
Total	23188	46009

Note: 30 µg includes data from phase 1 and phase 2/3.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:47)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s952

Table 19. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg		
Racial origin		
White	74	74
Black or African American	2	2
Asian	3	3
American Indian or Alaska Native	10	10

Table 19. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Total	89	89
Ethnic origin		
Hispanic/Latino	46	46
Non-Hispanic/non-Latino	43	43
Total	89	89

Note: 30 µg includes data from phase 1 and phase 2/3.
Note: Subjects who received 2nd Dose of BNT162b2 after unblinding.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:47)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2 unblinded/C4591001 PVP BLA/adsl s9523

Table 20. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg		
Racial origin		
White	16378	29671
Black or African American	1638	2912
Asian	852	1583
American Indian or Alaska Native	189	354
Native Hawaiian or other Pacific Islander	28	53
Multiracial	510	975
Not reported	101	187
Total	19696	35735
Ethnic origin		
Hispanic/Latino	5006	8141
Non-Hispanic/non-Latino	14580	27395
Not reported	110	199
Total	19696	35735

Note: 30 µg includes data from phase 1 and phase 2/3.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:47)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s952_open

Table 21. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 1 µg		
Racial Origin		
White	12	23
Total	12	23
Ethnic Origin		
Non-Hispanic/non-Latino	12	23
Total	12	23
Vaccine 3 µg		
Racial Origin		
White	12	24
Total	12	24
Ethnic Origin		
Non-Hispanic/non-Latino	12	24
Total	12	24
Vaccine 10 µg		
Racial Origin		
White	24	47
Total	24	47
Ethnic Origin		
Non-Hispanic/non-Latino	24	47
Total	24	47
Vaccine 20 µg		
Racial Origin		
White	24	48
Total	24	48
Ethnic Origin		
Non-Hispanic/non-Latino	24	48
Total	24	48
Vaccine 30 µg		
Racial Origin		
White	24	48
Total	24	48
Ethnic Origin		
Non-Hispanic/non-Latino	24	48
Total	24	48

Table 21. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses

Only race, ethnic origins collected on the case report form with a count of at least one in either column are displayed.
PFIZER CONFIDENTIAL SDTM Creation: 24NOV2020 (15:06) Source Data: adsl Table Generation: 10MAR2021 (12:27) (Cutoff date:23OCT2020, Snapshot Date: 23OCT2020)
Output File: ex_b2_dose_race rtf

Table 22. Exposure to BNT162b2 (30 µg) by Special Population (C4591001) – Blinded Placebo-Controlled Follow-up Period

Population	Number of Subjects Exposed to BNT162b2 (30 µg) (N[a]=23188) n[b]	Total Number of Vaccine Doses
Subjects with any baseline comorbidity	10371	26487
AIDS/HIV	100	196
Any Malignancy + Metastatic Solid Tumor + Leukemia + Lymphoma	852	1696
Chronic Pulmonary Disease	1901	3774
Renal Disease	140	279
Rheumatic Disease	75	147
Mild Liver Disease + Moderate or Severe Liver Disease	154	302
Cerebrovascular Disease + Peripheral Vascular Disease + Myocardial Infarction + Congestive Heart Failure	651	1298
Dementia	7	14
Diabetes With/Without Chronic Complication	1706	3385
Hemiplegia or Paraplegia	4	8
Peptic Ulcer Disease	63	126
Obese	7689	15262

Note: Comorbidity is based on Charlson Comorbidity Index categories. Participants identified as belonging to these categories were identified by medical history data collected during the study.
Note: 30 µg includes data from phase 1 and phase 2/3.
Note: Hemiplegia or Paraplegia only includes preferred terms Hemiplegia and Paraplegia.
a. N = number of subjects in the specified group.
b. n = Number of subjects reporting at least 1 occurrence of any comorbidity or obese (BMI ≥30 kg/m^2 [≥16 Years of age] or BMI ≥95th percentile [12-15 Years of age]).
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:25) Source Data: admh Table Generation: 27MAR2021 (12:47)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/admh_s953

Table 23. Exposure to BNT162b2 (30 µg) by Special Population (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Population	Number of Subjects Exposed to BNT162b2 (30 µg) (N[a]=19696) n[b]	Total Number of Vaccine Doses
Subjects with any baseline comorbidity	8981	21590
AIDS/HIV	86	161
Any Malignancy + Metastatic Solid Tumor + Leukemia + Lymphoma	734	1406
Chronic Pulmonary Disease	1590	2953
Renal Disease	139	262
Rheumatic Disease	66	122
Mild Liver Disease + Moderate or Severe Liver Disease	102	193
Cerebrovascular Disease + Peripheral Vascular Disease + Myocardial Infarction + Congestive Heart Failure	567	1075
Dementia	9	17
Diabetes With/Without Chronic Complication	1555	2928
Hemiplegia or Paraplegia	4	8
Peptic Ulcer Disease	76	145
Obese	6760	12320

Note: Comorbidity is based on Charlson Comorbidity Index categories. Participants identified as belonging to these categories were identified by medical history data collected during the study.
Note: 30 µg includes data from phase 1 and phase 2/3.
Note: Hemiplegia or Paraplegia only includes preferred terms Hemiplegia and Paraplegia.
a. N = number of subjects in the specified group.
b. n = Number of subjects reporting at least 1 occurrence of any comorbidity or obese (BMI ≥30 kg/m^2 [≥16 Years of age] or BMI ≥95th percentile [12-15 Years of age]).
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:25) Source Data: admh Table Generation: 27MAR2021 (12:47)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/admh_s953_open

2.1.2.a.2. Inclusion and Exclusion Criteria

Detailed descriptions of all inclusion and exclusion criteria for clinical studies are provided in the individual CSRs which were filed to IND 019736.

Inclusion criteria

- Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

- Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable infection with HIV, HCV, or HBV was permitted as the study progressed. Specific criteria for these Phase 3 participants can be found in the C4591001 protocol, Section 10.8.

- Phase 2/3 only: Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, front-line essential workers, and others).

- The participants enrolled were 12 years of age and older; the 12- to 15-year-old cohort was included in the protocol in October 2020.

Exclusion criteria

Phase 1 exclusion criteria were stricter than criteria in Phases 2 and 3 of the study. Participants were excluded from the studies according to the general criteria listed below:

- **Previous vaccination with any coronavirus vaccine**

  Reason for exclusion: To avoid confounding the assessment of serological or clinical immune response in the study population.

  Is it considered to be included as missing information? No.

  Rationale: Minimal potential clinical impact on the target population.

- **Previous clinical or microbiological diagnosis of COVID-19**

  Reason for exclusion: Phase 1 excluded participants with a previous clinical or microbiological diagnosis of COVID-19 because these participants may have some degree of protection from subsequent infection by SARS-CoV-2 and therefore would confound the pivotal efficacy endpoint. During Phase 2/3, participants with prior undiagnosed infection were allowed to be enrolled. Screening for SARS-CoV-2 with nucleic acid amplification test by nasal swab or antibodies to non-vaccine SARS-CoV-2

antigen by serology was not conducted before vaccine administration in Phase 2/3, but samples were taken to run these assays after vaccination, thus identifying participants with unidentified prior infection. This group will be assessed to identify whether prior infection affects safety.

Is it considered to be included as missing information? No.

Rationale: Safety in study participants with prior infection will be assessed in the pivotal study.

- **Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.**

  Reason for exclusion: Immunocompromised participants may have impaired immune responses to vaccines and would therefore limit the ability to demonstrate efficacy, which is the primary pivotal endpoint.

  Is it considered to be included as missing information? No.

  Rationale: Participants with potential immunodeficient status were not specifically included in the study population. However, since the study population is intended to be as representative as possible of the vulnerable population to COVID-19 illness, sub-analyses of immunogenicity data in future studies may provide further understanding of immune responses in this population.

- **Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study**

  Reason for exclusion: To avoid confounding the assessment of serological or clinical immune response in the study population.

  Is it considered to be included as missing information? No.

  Rationale: No impact on the safety of the target population.

- **Women who are pregnant or breastfeeding**

  Reason for exclusion: To avoid use in a vulnerable population.

  Is it considered to be included as missing information? Yes.

  Rationale: It is not known if maternal vaccination with BNT162b2 would have unexpected negative consequences to the embryo or fetus.

- **Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study**

  Reason for exclusion: To avoid misleading results deriving from non-compliance to study procedures.

  Is it considered to be included as missing information? No.

  Rationale: Safety profile of BNT162b2 is not expected to differ in these subjects when properly administered.

2.1.2.a.2.1. Non-Study Post-Authorization Exposure

It is not possible to determine with certainty the number of individuals who received BNT162b2 since it was first authorized for emergency use on 01 December 2020. Estimated worldwide shipped doses may serve as a reasonable indicator of subject exposure by region and countries; the estimated exposure by gender and age group is not available. Cumulatively, through the DLP (28 February 2021) approximately 126,212,580 doses of BNT162b2 were shipped worldwide. The estimated cumulative number of shipped doses of BNT162b2 by region, are summarized in Table 24.

Table 24. Cumulative Estimated Shipped Doses[a] of BNT162b2 by Region Worldwide

Region/Country	Total Number of Shipped Doses	% of Doses
Europe	**51,545,325**	**40.8%**
European Union (27)	36340590	28.8%
European Free Trade Association (3)	513825	0.4%
Switzerland	767520	0.6%
UK	13643175	10.8%
Other Countries	280215	0.2%
Commonwealth of Independent States[b]	0	**0.0%**
North America	**56577885**	**44.8%**
US	54326415	43.0%
Canada	2251470	1.8%
Central and South America	**2965170**	**2.3%**
Asia	**14467830**	**11.5%**
Oceania	**656370**	**0.5%**
Africa	**0**	**0.0%**
Total	**126,212,580**	**100.0%**

a. Data for US are based on Order Management Dashboard, while for the remaining Regions and Countries are based on the Order Book which is the most accurate tracker of shipment data.
b. Includes: Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Ukraine, Uzbekistan;

Method Used to Calculate Exposure

Not applicable.

Exposure

Not applicable.

2.1.2.a.3. Regulatory Actions Related to Safety

There were no withdrawals for safety reasons up to 28 February 2021.

2.1.2.b. Populations Not Studied in the Pre-Approval Phase

There has been limited exposure to BNT162b2 in some special populations and no epidemiologic studies have been conducted in pregnant/lactating women, pediatric participants (<12 years of age), and specific subpopulations that were initially excluded from the BNT162b2 program.

Table 25. Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of special population	Exposure
Pregnant women	Available data on BNT162b2 administered to pregnant women are insufficient to inform on vaccine-associated risks in pregnancy. In a reproductive and developmental toxicity study, no vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported. Through the cut-off date of 13 March 2021, there were 50 cases (52 events) originating from Study C4591001 in participant 16 years of age and older, and all were unique pregnancies.
Breastfeeding women	Breastfeeding women were not initially included in the BNT162b2 clinical development program. Data are not available to assess the effects of BNT162b2 on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BNT162b2 and any potential adverse effects on the breastfed child from BNT162b2 or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptible to disease prevented by the vaccine. Through the cut-off date of 13 March 2021, there were no CT cases indicative of exposure during breastfeeding from study C4591001 in participants 16 years of age and older.
Participants with relevant comorbidities: • Participants with hepatic impairment • Participants with renal impairment • Participants with cardiovascular disease • Immunocompromised participants • Participants with a disease severity different from inclusion criteria in CTs	Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included. This allowed enrollment of a proportion of participants with common comorbidities such as cardiovascular diseases including hypertension, chronic pulmonary diseases, asthma, chronic liver disease, BMI >30 kg/m^2, participants with stage 3 or worse chronic kidney disease, and participants with varying disease severity. Participants with potential immunodeficient status were not specifically included in the study population. Please refer to Table 22 and Table 23 for the exposure of special populations.

Table 25. Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of special population	Exposure
Participants of different racial and/or ethnic origin	Please refer to Table 21 for exposure information by ethnic origin from the studies.
Subpopulations carrying known and relevant polymorphisms	No data available.
Pediatric participants	The safety and effectiveness of BNT162b2 in individuals younger than 16 years of age have not been established. **Participants 16 years of age and older** A total of 671 pediatric participants 16 to 17 years of age received BNT162b2 through the DLP of 13 March 2021: • 378 participants in the blinded-placebo controlled follow-up period (Table 3). • 293 participants in the open-label follow-up period after the unblinding (Table 5). **Participants 12 to 15 years of age** One thousand and hundred eighty (1180) pediatric participants 12 to 15 years of age received BNT162b2 through the cut-off date of 13 March 2021 (Table 3 and Table 5).
Elderly (≥65 years old)	The safety and effectiveness of BNT162b2 in elderly participants was consistent with that seen in younger adult participants. Clinical studies of BNT162b2 included a total of 8846 participants 65 years of age and over; of these, 8827 were from study C4591001, through the cut-off date of 13 March 2021: • 4590 participants in the blinded-placebo controlled follow-up period (Table 3) • 4237 participants in the open-label follow-up period after unblinding (Table 5). Nineteen (19) participants 65 years of age and over were from study BNT162-01 study through the cut-off date of 23 October 2020 (Table 6).

Abbreviations: EUA = emergency use authorization; BMI = body mass index; COVID-19 = coronavirus disease 2019; CT = clinical trial

2.1.2.c. Adverse Events / Adverse Reactions

2.1.2.c.1. Identification of Safety Concern in the Initial PVP Submission

2.1.2.c.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the PVP

Not all potential or identified risks for the vaccine are considered to meet the level of importance necessitating inclusion in the list of safety concerns in the PVP:

- Risks with minimal and temporary clinical impact on patients (in relation to the severity of the disease prevented).

- The following reactogenicity events are identified risks not included in the list of safety concerns in the PVP: Injection site pain, Fever, Chills, Fatigue, Headache, Muscle pain, and Joint pain.

- Very rare potential risks for any medicinal treatment, including vaccines which are well known to healthcare professionals are not included in the list of safety concerns.

2.1.2.c.2. Important Identified and Potential Risks and Missing Information

2.1.2.c.2.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks

Table 26. Myocarditis and Pericarditis

Potential mechanisms, evidence source and strength of evidence	A mechanism of action (MOA) by which the vaccine could cause myocarditis and pericarditis has not been established. Nonclinical studies, protein sequence analyses and animal studies in rats and non-human primates have not identified a MOA. Hypotheses for MOA include an immune stimulated response (including the possibility of molecular mimicry), a general systemic inflammatory response from vaccination or a hypersensitivity response.
Characterisation of the risk	***Participants 16 years of age and older*** Data from the CT dataset Two cases were retrieved with the myocarditis and pericarditis search strategy[a] in the clinical trial dataset through the cut-off date of 18 June 2021. These cases originated from Phase 3 clinical study C4591001 and are summarized below: Myocarditis: There were no cases reporting myocarditis as SAE. Pericarditis (2 cases): Two (2) serious adverse events [PT Pericarditis] were reported, both deemed not related to study treatment by the Investigator. Data from the safety database: Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 18 June 2021, 823 potentially relevant cases (0.3% of the total post-authorization dataset) were retrieved from the Myocarditis and Pericarditis search strategy:[a] 490 cases reported events related to myocarditis and 371 cases reported events related to pericarditis (in 38 of these 823 cases, the subjects developed both myocarditis and pericarditis related events). Myocarditis (490 cases): These 490 cases were individually reviewed and assessed according to Brighton Collaboration (BC) Myocarditis Case Definition and Level of Certainty Classification (version 1.4.2, 30 May 2021), as shown in the Table below:

Brighton Collaboration Level	Number of cases
BC 1	41
BC 2	44

Table 26. Myocarditis and Pericarditis

BC 3	42
BC 4	337
BC 5	26
Total	490

Level 1 indicates a definitive case with the highest level of diagnostic certainty of myocarditis, level 2 indicates a probable case, and level 3 indicates a possible case. Level 4 is defined as "reported event of myocarditis with insufficient evidence to meet the case definition" and Level 5 as not a case of myocarditis.

There were 464 cases meeting BC Level 1 to 4, which are presented below:

Country of incidence: Israel (135), US (78), Germany (76), UK (55), France (21), Italy, Japan (13 each), Austria (10), Greece, Spain (8 each), Sweden (7), Canada, Norway (6 each), Ireland (5); the remaining 23 cases originated from 17 different countries.

Gender: Females (133), Males (325), Unknown (6).

Age (n=443) ranged from 16 to 97 years (mean = 37.2 years, median = 32.0 years).

Reported relevant PTs: Myocarditis (463) and Autoimmune myocarditis (1).

Overall event seriousness and outcome of these 464 cases are summarized below.

	Total Events N = 464 (%)
Serious events	459 (98.9)
Events with Criterion of Hospitalization	337 (72.6)
Distribution of events by Outcome	
Outcome: Death	14 (3.0)
Outcome: Resolved/Resolving	149 (32.1)
Outcome: Not resolved	106 (22.8)
Outcome: Resolved with sequelae	10 (2.2)
Outcome: Unknown/No data	185 (39.9)

Pericarditis (371 cases)

Country of incidence: US (68), France (62), Israel (50), UK (38), Italy (33), Norway, Spain (24 each), Canada (10), Australia (9), Greece (7), Germany (6), Belgium, Denmark, Netherlands, Switzerland (5 each); the remaining 20 cases originated from 11 different countries.

Gender: Females (185), Males (181), Unknown (5).

Age (n=335) ranged from 16 to 92 years (mean = 51.5 years, median = 51.0 years).

Reported relevant PTs: Pericarditis (360) and Pleuropericarditis (12).

Overall event seriousness and outcome of these 371 cases are summarized below.

	Total Events N = 372 (%)
Serious events	370 (99.5)
Events with Criterion of Hospitalization	206 (55.4)
Distribution of events by Outcome	

Table 26. Myocarditis and Pericarditis

Outcome: Death	3 (0.8)
Outcome: Resolved/Resolving	213 (57.3)
Outcome: Not resolved	63 (16.9)
Outcome: Resolved with sequelae	7 (1.9)
Outcome: Unknown/No data	86 (23.1)

Participants 12 to 15 years of age

Data from the CT dataset:
No cases were retrieved reporting Myocarditis and Pericarditis as SAE in the clinical trial dataset through the cut-off date of 18 June 2021.

Data from the safety database:
Through 18 June 2021, 15 potentially relevant cases were retrieved from the Myocarditis and Pericarditis search strategy:[a] 13 cases reported myocarditis and 4 cases reported pericarditis (in 2 of these 15 cases, the subjects developed both myocarditis and pericarditis).

Myocarditis (13 cases)

These 13 cases were individually reviewed and assessed according to Brighton Collaboration (BC) Myocarditis Case Definition and Level of Certainty Classification, as shown in the Table below:

Brighton Collaboration Level	Number of cases
BC 1	0
BC 2	0
BC 3	0
BC 4	11
BC 5	2
Total	13

Level 1 indicates a definitive case with the highest level of diagnostic certainty of myocarditis, level 2 indicates a probable case, and level 3 indicates a possible case. Level 4 is defined as "reported event of myocarditis with insufficient evidence to meet the case definition" and Level 5 as not a case of myocarditis.

No cases met BC levels 1 to 3. There were 11 cases meeting BC Level 4, which are presented below:

Country of incidence: US (10) and Bahrain (1).
Gender: Female (1), Males (10).

Age (n=11) ranged from 12 to 15 years (mean = 13.8 years, median = 14.0 years).

Reported relevant PT: Myocarditis (11).

Overall event seriousness and outcome of these 11 cases are summarized below.

	Total Events N = 11
Serious events	10
Events with Criterion of Hospitalization	9

Table 26. Myocarditis and Pericarditis

<table>
<tr><td></td><td>
<table>
<tr><td colspan="2">Distribution of events by Outcome</td></tr>
<tr><td>Outcome: Death</td><td>0</td></tr>
<tr><td>Outcome: Resolved/Resolving</td><td>3</td></tr>
<tr><td>Outcome: Not resolved</td><td>4</td></tr>
<tr><td>Outcome: Resolved with sequelae</td><td>0</td></tr>
<tr><td>Outcome: Unknown/No data</td><td>4</td></tr>
</table>

<u>Pericarditis (4 cases)</u>
Country of incidence: US (4).
Gender: Males (4).
Age (n=4) ranged from 12 to 15 years (mean = 13.5 years, median = 13.5 years).
Reported relevant PT: Pericarditis (4).

Overall event seriousness and outcome of these 4 cases are summarized below.

<table>
<tr><td></td><td>Total Events
N = 4</td></tr>
<tr><td>Serious events</td><td>3</td></tr>
<tr><td>Events with Criterion of Hospitalization</td><td>1</td></tr>
<tr><td colspan="2">Distribution of events by Outcome</td></tr>
<tr><td>Outcome: Death</td><td>0</td></tr>
<tr><td>Outcome: Resolved/Resolving</td><td>1</td></tr>
<tr><td>Outcome: Not resolved</td><td>1</td></tr>
<tr><td>Outcome: Resolved with sequelae</td><td>0</td></tr>
<tr><td>Outcome: Unknown/No data</td><td>2</td></tr>
</table>
</td></tr>
<tr><td>Risk factors and risk groups</td><td>Post-authorization reports have been received for more males than females, over a wide age range and following dose 1 and dose 2 of the vaccine. Evaluation by the US CDC has found reports to be most frequent in adolescent and young adult male patients following the second dose of vaccine.</td></tr>
<tr><td>Preventability</td><td>Due to an unknown MOA, preventative measures are not clear for individuals with or without a personal history of myocarditis or pericarditis.</td></tr>
<tr><td>Impact on the risk-benefit balance of the biologic product</td><td>The vaccine continues to have a favorable risk benefit balance</td></tr>
<tr><td>Public health impact</td><td>Considering the low rates of myocarditis and pericarditis reported following vaccination, balanced with the risk of death and illness (including myocarditis) caused by SARS-CoV-2, the public health impact of post-vaccination myocarditis and pericarditis is minimal.</td></tr>
</table>

a. Search criteria: the following PTs were used to retrieve cases of Myocarditis and Pericarditis: Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis; Autoimmune pericarditis, Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.
Please note that CT dataset from the safety dabase includes only cases reporting SAEs.

Table 27. Anaphylaxis

<table>
<tr><td>Potential mechanisms, evidence source and strength of evidence</td><td>Interaction of an allergen with IgE on basophils and mast cells triggers release of histamine, leukotrienes and other mediators that cause diffuse smooth muscle contraction and vasodilation with plasma leakage. This can manifest clinically with dyspnea, hypotension, swelling (sometimes leading to airway compromise), and rash (including hives).</td></tr>
<tr><td>Characterisation of the risk</td><td>
<u>Data from the CT database</u>

Information pertinent to the anaphylactic reactions observed participants 16 years and older in the ongoing Phase 3 clinical study C4591001 through the cut-off date of 13 March 2021, are summarized below:

Five (5) serious events [Acute respiratory failure, Cardiac arrest, Anaphylactic reaction, Anaphylactoid reaction (post bee sting), and Anaphylactic shock] were reported. The Anaphylactoid reaction, occurred to a participant in the age group 16-55 years, was assessed as related to study treatment by the Investigator. The remaining 4 events were deemed not related to study treatment by the Investigator.

<u>Data from the safety database:</u>

Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, 1833 potentially relevant cases[b], were retrieved from the Anaphylactic reaction SMQ (Narrow and Broad) search strategy, applying the MedDRA algorithm. These 1833 cases were individually reviewed and assessed according to Brighton Collaboration (BC) definition and level of diagnostic certainty as shown in the Table below:
<table>
<tr><th>Brighton Collaboration Level</th><th>Number of cases</th></tr>
<tr><td>BC 1</td><td>290</td></tr>
<tr><td>BC 2</td><td>311</td></tr>
<tr><td>BC 3</td><td>10</td></tr>
<tr><td>BC 4</td><td>391</td></tr>
<tr><td>BC 5</td><td>831</td></tr>
<tr><td>Total</td><td>1833</td></tr>
</table>
Level 1 indicates a case with the highest level of diagnostic certainty of anaphylaxis, whereas the diagnostic certainty is lowest for Level 3. Level 4 is defined as “reported event of anaphylaxis with insufficient evidence to meet the case definition” and Level 5 as not a case of anaphylaxis.

There were 1002 cases (54.0% of the potentially relevant cases retrieved), 2958 potentially relevant events, from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy, meeting BC Level 1 to 4. Country of incidence: UK (261), US (184), Mexico (99), Italy (82), Germany (67), Spain (38), France (36), Portugal (22), Denmark (20), Finland, Greece (19 each), Sweden (17), Czech Republic, Netherlands (16 each), Belgium, Ireland (13 each), Poland (12), Austria (11); the remaining 57 cases originated from 15 different countries.
Gender: Females (876), Males (106), Unknown (20);
Age (n=961) ranged from 16 to 98 years (mean = 54.8 years, median = 42.5 years);

Overall event seriousness and outcome of these 1002 cases are summarized below.
<table>
<tr><th></th><th>Total Events
N = 2958 (%)</th></tr>
<tr><td>Serious events</td><td>2341 (79.1)</td></tr>
<tr><td>Events with Criterion of Hospitalization</td><td>752 (25.4)</td></tr>
<tr><td colspan="2">Distribution of events by Outcome*</td></tr>
</table>
</td></tr>
</table>

Table 27. Anaphylaxis

	Outcome∞: Death§ 9 (0.3) Outcome: Resolved/Resolving 1922 (65.0) Outcome: Not resolved 229 (7.7) Outcome: Resolved with sequelae 48 (1.6) Outcome: Unknown/No data 754 (25.5) * For the outcome count, the multiple Lowest Level Terms that code to the same PT within a case are counted and presented individually. Therefore, for selected PTs the total count of the event outcome may exceed the total number of events. ∞ Different clinical outcomes may be reported for an event occurred more than once to the same individual. § There were 4 individuals in the anaphylaxis evaluation who died on the same day they were vaccinated. Although these patients experienced adverse events (9) that are potential symptoms of anaphylaxis, they all had serious underlying medical conditions, and one individual appeared to also have COVID-19 pneumonia, that likely contributed to their deaths. The most frequently reported relevant PTs (≥2%), from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy were: Anaphylactic reaction (435), Dyspnoea (356), Rash (190), Pruritus (175), Erythema (159), Urticaria (133), Cough (115), Respiratory distress, Throat tightness (97 each), Swollen tongue (93), Anaphylactic shock (80), Hypotension (72), Chest discomfort (71), Swelling face (70), Pharyngeal swelling (68), and Lip swelling (64). Conclusion: Evaluation of BC cases Level 1 – 4 did not reveal any significant new safety information. Anaphylaxis is appropriately described in the product labeling as are non-anaphylactic hypersensitivity events. Surveillance will continue.
Risk factors and risk groups	Known hypersensitivity to any components of the vaccine.
Preventability	Prevention of anaphylaxis may not be possible, particularly with the 1st dose of a vaccine; therefore, healthcare professionals administering the vaccine must be vigilant for early signs and symptoms.
Impact on the risk-benefit balance of the biologic product	Anaphylactic reaction in an individual can be impactful (medically important) because it is a potentially life-threatening event requiring medical intervention.
Public health impact	Minimal due to rarity of the event. Although the potential clinical consequences of an anaphylactic reaction are severe, this is a known risk of vaccines to healthcare professionals with negligible public health impact.

b. Search criteria Anaphylactic reaction SMQ (Narrow and Broad, with the MedDRA algorithm applied), with relevant cases assessed according to Brighton Collaboration (BC) criteria.

Important Potential Risks

Table 28. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

<table>
<tr><td>Potential mechanisms, evidence source and strength of evidence</td><td>This potential risk is theoretical because it has not been described in association with the BNT162b2 or it has not been reported from any other late phase clinical trial of other human vaccine. Animal models of SARS-CoV-2 infection have not shown evidence of VAED after immunization, whereas cellular immunopathology has been demonstrated after viral challenge in some animal models administered SARS-CoV-1 (murine, ferret and non-human primate models) or MERS-CoV (mice model) vaccines.[1,6] This potential risk has been included based on these animal data with these related betacoronaviruses. Historically, disease enhancement in vaccinated children following infection with natural virus has been observed with an inactivated respiratory syncytial virus vaccine.[7]
Potential mechanisms of enhanced disease may include both T cell-mediated [an immunopathological response favoring T helper cell type 2 (T_H2) over T helper cell type 1 (T_H1)] and antibody-mediated activity (antibody responses with insufficient neutralizing activity leading to formation of immune complexes and activation of complement or allowing for Fc-mediated increase in viral entry to cells).[8]</td></tr>
<tr><td>Characterization of the risk</td><td>Data from the CT database (Participant 16 years and older)
Confirmed Case of Postvaccination Severe COVID-19 – Blinded Placebo-Controlled Follow-up Period - Safety Population (C4591001)
<table><tr><th></th><th colspan="2">BNT162b2 (30 µg) (N[a]=23164)</th><th colspan="2">Placebo (N[a]=23155)</th></tr><tr><th>Timing</th><th>n[b] (%)</th><th>(95% CI[c])</th><th>n[b] (%)</th><th>(95% CI[c])</th></tr><tr><td>PD1 Before Dose 2</td><td>0</td><td>(0.0, 0.0)</td><td>6 (0.0)</td><td>(0.0, 0.0)</td></tr><tr><td>Within 7 days PD1</td><td>0</td><td>(0.0, 0.0)</td><td>0</td><td>(0.0, 0.0)</td></tr><tr><td>PD2</td><td>1 (0.0)</td><td>(0.0, 0.0)</td><td>25 (0.1)</td><td>(0.1, 0.2)</td></tr><tr><td>Within 7 days PD2</td><td>0</td><td>(0.0, 0.0)</td><td>2 (0.0)</td><td>(0.0, 0.0)</td></tr><tr><td>Total[d]</td><td>1 (0.0)</td><td>(0.0, 0.0)</td><td>31 (0.1)</td><td>(0.1, 0.2)</td></tr></table>Note: This table includes subjects from Phase 2/3 only.
Abbreviations: PD1 = post-dose 1; PD2 = post-dose 2.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Total is the sum of PD1 and PD2.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adc19ef Table Generation: 27MAR2021 (12:47) (Cutoff date: 13MAR2021, Snapshot Date: 25MAR2021)
Output File: /nda2_unblinded/C4591001_PVP_BLA/adeff_s901

If VAED/VAERD were to occur in vaccinated individuals, it may manifest as a modified and/or more severe clinical presentation of SARS-CoV-2 viral infection upon subsequent natural infection. This may result in individuals assumed to be at lower risk for severe COVID-19 having more severe disease, for individuals at known risk for severe COVID-19 (e.g. older or immunocompromised) having higher rates of fatal outcomes, or for observation of an unfavorable imbalance in severe COVID-19</td></tr>
</table>

Table 28. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

cases in vaccinated individuals when compared to those not vaccinated. It is challenging to assess for VAED/VAERD on an individual case basis, given the lack of specific clinical or laboratory markers at this time, rather surveillance for this theoretical risk is best performed at a population level,[9] as noted above. The table above shows a favorable balance of severe COVID-19 cases in participants receiving BNT162b2 versus those receiving placebo, providing reassurance against the potential risk of VAED/VAERD at this time.

Data from the safety database

No post-authorized AE reports have been identified as cases of VAED/VAERD, therefore, there is no observed data at this time. An expected rate of VAED is difficult to establish so a meaningful observed/expected analysis cannot be conducted at this point based on available data. The feasibility of conducting such an analysis will be re-evaluated on an ongoing basis as data on the virus grows and the vaccine safety data continues to accrue.

The search criteria utilised to identify potential cases of VAED for this report includes PTs indicating a lack of effect of the vaccine and PTs potentially indicative of severe or atypical COVID-19[a].

Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, the following numbers of potentially relevant cases were retrieved:

138 cases [0.25% of the total post-authorization dataset], reporting 317 potentially relevant events.
Seriousness criteria for the total 138 cases: Medically significant (71, of which 8 also serious for disability), Hospitalization required (non-fatal/non-life threatening) (16, of which 1 also serious for disability), Life threatening (13, of which 7 were also serious for hospitalization), Death (38).
Gender: Females (73), Males (57), Unknown (8).
Age (n=132) ranged from 21 to 100 years (mean = 57.2 years, median = 59.5).

Overall event seriousness and outcome are summarized below.

	Total Events N = 317 (%)
Serious events	279 (88.0)
Events with Criterion of Hospitalization	91 (28.7)
Distribution of events by Outcome[a]	
Outcome: Death	62 (19.6)
Outcome: Resolved/Resolving	61 (19.2)
Outcome: Not resolved	90 (28.4)
Outcome: Resolved with sequelae	1 (0.3)
Outcome: Unknown/No data	106 (33.4)

a. For the outcome count, the multiple Lowest Level Terms that code to the same PT within a case are counted and presented individually. Therefore, for selected PTs the total count of the event outcome may exceed the total number of events.

The most frequently reported relevant PTs (≥5 events) were: Drug ineffective (135), Dyspnoea (53), Diarrhoea (30), COVID-19 pneumonia (23), Vomiting (20), Respiratory failure (8), Seizure (7), Hypoxia (6), Abdominal pain, and Pulmonary embolism (5 each).

Table 28. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

	Conclusion: VAED may present as severe or unusual clinical manifestations of COVID-19. Overall, there were 37 subjects with suspected COVID-19 and 101 subjects with confirmed COVID 19 following one or both doses of the vaccine; 75 of the 101 cases were severe, resulting in hospitalisation, disability, life threatening consequences or death. None of the 75 cases could be definitively considered as VAED/VAERD. In this review of subjects with COVID-19 following vaccination, based on the current evidence, VAED/VAERVAED remains a theoretical risk for the vaccine. Surveillance will continue.
Risk factors and risk groups	It is postulated that the potential risk may be increased in individuals producing lower neutralizing antibody titers or in those demonstrating waning immunity.[8,9]
Preventability	An effective vaccine against COVID-19 that produces high neutralizing titers and a T_H1 predominant $CD4^+$ T cell response and strong $CD8^+$ T cell response, is expected to mitigate the risk of VAED/VAERD;[1,8] that immune profile is elicited by BNT162b2 in clinical and preclinical studies.[10,11]
Impact on the risk-benefit balance of the biologic product	If there were an unfavorable balance in COVID-19 cases, including severe cases, in the pivotal clinical study between the vaccine and placebo groups, that may signal VAED/VAERD.
Public health impact	The potential risk of VAED/VAERD could have a public health impact if large populations of individuals are affected.

a. Standard Decreased Therapeutic Response Search AND at least 1 of the following PTs Dyspnoea; Tachypnoea; Hypoxia; COVID 19 pneumonia; Respiratory Failure; Acute Respiratory Distress Syndrome; Cardiac Failure; Cardiogenic shock; Acute myocardial infarction; Arrhythmia; Myocarditis; Vomiting; Diarrhoea; Abdominal pain; Jaundice; Acute hepatic failure; Deep vein thrombosis; Pulmonary embolism; Peripheral Ischaemia; Vasculitis; Shock; Acute kidney injury; Renal failure; Altered state of consciousness; Seizure; Encephalopathy; Meningitis; Cerebrovascular accident; Thrombocytopenia; Disseminated intravascular coagulation; Chillblains; Erythema multiforme; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome in children.
Note: the "Standard Decreased Therapeutic Response" search includes the Lack of efficacy PTs (Drug ineffective/Vaccination failure).

2.1.2.c.2.2. Presentation of Missing Information

Table 29. Use in Pregnancy and Lactation

Evidence source:
The safety profile of the vaccine is not known in pregnant or lactating women due to their exclusion from the pivotal clinical study. There may be pregnant women who choose to be vaccinated despite the lack of safety data. It will be important to follow these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favorable or unfavorable impacts on the embryo/fetus. The clinical consequences of SARS-CoV-2 infection to the woman and fetus during pregnancy is not yet fully understood and the pregnant woman's baseline health status may affect both the clinical course of her pregnancy and the severity of COVID-19 disease. These factors and the extent to which the pregnant woman may be at risk of exposure to SARS-CoV-2 will influence the benefit risk considerations for use of the vaccine.

Population in need of further characterization:
The lack of data will be communicated in product labeling; one clinical study of the safety and immunogenicity of the BNT162b2 in pregnant women is ongoing (C4591015); 2 non-interventional studies (C4591009 and C4591011) to assess whether sub-cohorts of interest, such as pregnant women, experience increased risk of safety events of interest following receipt of the BNT162b2 are planned (see 3.1.3 – *Action plan for safety issues*).

Data from the Safety Database[a]
Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, there were 413 cases (1.0 % of the total Post-authorization dataset) reporting use during pregnancy or lactation.

Overall event seriousness and outcome are summarized below:

	Total Events N = 1122 (%)
Serious events	270 (24.1)
Events with Criterion of Hospitalization	14 (1.2)
Distribution of events by Outcome*	
Outcome: Death§	5 (0.4)
Outcome: Resolved/Resolving	205 (18.3)
Outcome: Not resolved	64 (5.7)
Outcome: Resolved with sequelae	4 (0.4)
Outcome: Unknown/No data	849 (75.7)

* For the outcome count, the multiple Lowest Level Terms that code to the same PT within a case are counted and presented individually. Therefore, for selected PTs the total count of the event outcome may exceed the total number of events.
§ Two babies whose mothers were vaccinated during their second trimester of gestation, were pre-maturely delivered 5 days after vaccination and died on their second day of life.

The most frequently reported relevant PTs (≥2%) were: Maternal exposure during pregnancy (187), Product use issue (148), Off label use (147), Exposure via breast milk (133), Exposure during pregnancy (55), Headache (33), Abortion spontaneous (25), Vaccination site pain (24), Pain in extremity, Pyrexia (23 each) and Fatigue (22).

a. Cumulative RMP tables on Missing information are provided as per FDA's request to include a cumulative analysis, from post-authorization experience, of the Important Missing Information identified in the Pharmacovigilance Plan. More detailed information is available in the cumulative analysis of post-authorization data provided as a standalone document with the BLA submission.

Table 30. Vaccine Effectiveness

Evidence source:

Although vaccine efficacy in a controlled clinical study is the objective of the pivotal study, real-world vaccine effectiveness when the BNT162b2 is used in a large and more diverse population is unknown.

Anticipated risk/consequence of missing information:

Efficacy information obtained from clinical study data will be communicated in the product labeling. Three post-authorization effectiveness studies in real-world use are planned: 1 non-interventional study (C4591014) and 2 low-interventional studies (WI235284 and WI255886) to determine the effectiveness of BNT162b2 when administered outside of the clinical setting (see 3.1.3 – *Action plan for safety issues*).

Data from the Safety Database[a]

Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, there were 1665 cases (3.9% of the total Post-authorization dataset) reporting lack of efficacy.

Overall event seriousness and outcome are summarized below:

	Total Events N = 1665 (%)
Serious events	1644 (98.7)
Events with Criterion of Hospitalization	65 (3.9)
Distribution of events by Outcome*	
Outcome: Death	65 (4.0)
Outcome: Resolved/Resolving	164 (9.8)
Outcome: Not resolved	205 (12.3)
Outcome: Resolved with sequelae	0 (0)
Outcome: Unknown/No data	1231 (73.9)

* For the outcome count, the multiple Lowest Level Terms that code to the same PT within a case are counted and presented individually. Therefore, for selected PTs the total count of the event outcome may exceed the total number of events.

The PT Drug ineffective was reported in 1646 cases, Vaccination failure was reported in 19 cases; the most frequently co-reported PTs (≥2%) were: COVID 19 (1244), SARS-CoV-2 test positive(219), Suspected COVID-19 (161), Pyrexia (134), and Headache (110).

a. Cumulative RMP tables on Missing information are provided as per FDA's request to include a cumulative analysis, from post-authorization experience, of the Important Missing Information identified in the Pharmacovigilance Plan. More detailed information is available in the cumulative analysis of post-authorization data provided as a standalone document with the BLA submission.

Table 31. Use in Paediatric Individuals <12 Years of Age

Evidence source:
BNT162b2 has not been initially studied in pediatric individuals younger than 12 years of age due to their exclusion from the pivotal clinical study.

Paediatric individuals may display different reactogenicity and safety profiles compared to adults, due to lower body mass and differently matured immunological responses.

Population in need of further characterization:
The are no data in individuals less than 12 years of age; a clinical study of the safety, tolerability, immunogenicity and efficacy of BNT162b2 in individuals younger than 12 years [C4591007 (< 12 years of age)][a] is ongoing (see 3.1.3 – *Action plan for safety issues*); a non-interventional study (C4591009) is planned to assess the occurrence of safety events of interest in a general US population (< 12 and ≥ 12 to ≤15 years of age) (see 3.1.3 – *Action plan for safety issues*).

Data from the Safety Database[b]
Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, there were 34 cases (0.08% of the total Post-authorization dataset) involving individuals below 12 years of age.
Overall event seriousness and outcome are summarized below:

	Total Events N = 132 (%)
Serious events	66 (50)
Events with Criterion of Hospitalization	19 (14.4)
Distribution of events by Outcome*	
Outcome: Death	0
Outcome: Resolved/Resolving	25 (18.9)
Outcome: Not resolved	42 (31.8)
Outcome: Resolved with sequelae	0
Outcome: Unknown/No data	65 (49.2)

* For the outcome count, the multiple Lowest Level Terms that code to the same PT within a case are counted and presented individually. Therefore, for selected PTs the total count of the event outcome may exceed the total number of events.

The most frequently reported PTs (≥2%) were: Product administered to patient of inappropriate age (27), Off label use (11), Pyrexia (6), Product use issue (5), Fatigue, Headache, Nausea (4 each) and Vaccination site pain (3).

a. 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 RNA vaccine candidate against COVID 19 in healthy children <12 years of age.
b. Cumulative RMP tables on Missing information are provided as per FDA's request to include a cumulative analysis, from post-authorization experience, of the Important Missing Information identified in the Pharmacovigilance Plan. More detailed information is available in the cumulative analysis of post-authorization data provided as a standalone document with the BLA submission.

2.1.2.d. Identified and Potential Interactions, Including Food-Biologic Product and Drug-Biologic Product Interactions

As noted in the WHO Guidelines on Nonclinical Evaluation of Vaccines,[3] pharmacokinetics testing is not required for final formulation. No interaction linked to metabolism is expected with vaccines. The only potential for interaction is with other vaccines administered concomitantly and with immunosuppressive drugs.

Co-administration studies with BNT162b2 have not been done, therefore there is not sufficient data to understand the effect on vaccine effectiveness of BNT162b2 or co-administered vaccines. A co-administration study with seasonal influenza vaccine is planned. If BNT162b2 is given at the same time as other injectable vaccine(s), the vaccine(s) should be administered at different injection sites.

2.1.2.e. Epidemiology of Indication and Target Population

Indication

Active immunization against COVID-19 disease caused by SARS-CoV-2 virus in individuals ≥ 16 years of age.

Incidence:

The COVID-19 is caused by a novel coronavirus labeled as SARS-CoV-2. The disease first emerged in December 2019, when a cluster of patients with pneumonia of unknown cause was recognized in Wuhan City, Hubei Province, China.[12] The number of infected cases rapidly increased and spread beyond China throughout the world. On 30 January 2020, the WHO declared COVID-19 a Public Health Emergency of International Concern and thus a pandemic.[13]

Estimates of SARS-CoV-2 incidence change rapidly. We obtained incidence and prevalence estimates using data from Worldometer, a trusted independent organization that collects COVID-19 data from official reports and publishes current global and country-specific statistics online.[14]

As of 03 March 2021, the overall number of people who had been infected with SARS-CoV-2 was over 115 million worldwide,[15] an increase of nearly 100 million in the 7 months since 28 July 2020.[16] Table 32 shows the incidence and prevalence as of 03 March 2021 for the US, UK, and EU-27 countries. In the EU and the UK, by 03 March 2021 the total number of confirmed cases had accumulated to almost 27 million people, or 5,226 per 100,000 people (from 1.7 million, or 337 per 100,000 by 28 July 2020). Across countries in the EU, the number of confirmed cases ranged from 1,072 to 11,836 cases per 100,000 people. Finland and Greece reported the lowest incidence rates while Czech Republic, Slovenia, and Luxembourg reported the highest.[15]

In the US, the number of confirmed cases had reached over 29 million (8,864 per 100,000 people) by 03 March 2021.[15] This is an increase from 4.5 million (1,357 per 100,000) by 28 July 2020.[17]

Table 32. Incidence, Prevalence, and Mortality of COVID-19 as of 03 March 2021 [15]

	Total Cases	Incidence: Total Cases/ 100,000	Active Cases[a]	Prevalence: Active Cases/ 100,000	Total Deaths	Mortality: Deaths / 100,000	Population
Global	115,760,943	1,485	21,707,680	278	2,571,518	33	7,794,824,793
EU-27	22,642,536	5,083	6,113,464	1,462	553,363	124	445,424,167
UK	4,194,785	6,157	1,065,282	1,564	123,783	182	68,125,249
EU-27 + UK	26,837,321	5,226	7,178,746	1,398	677,146	132	513,549,416
US	29,456,377	8,864	8,921,400	2,685	531,652	160	332,304,437
EU-27 Countries							
Austria	465,322	5,147	21,028	233	8,625	95	9,040,866
Belgium	774,344	6,662	699,566	6,019	22,141	191	11,623,476
Bulgaria	253,183	3,662	33,770	488	10,413	151	6,913,156
Croatia	244,205	5,973	3,322	81	5,555	136	4,088,197
Cyprus	35,620	2,936	33,331	2,747	232	19	1,213,250
Czech Republic	1,269,058	11,836	154,580	1,442	20,941	195	10,722,330
Denmark	212,798	3,665	6,995	120	2,370	41	5,805,897
Estonia	69,193	5,214	17,938	1,352	615	46	1,327,135
Finland	59,442	1,072	12,683	229	759	14	5,546,504
France	3,810,316	5,829	3,461,485	5,295	87,542	134	65,370,546
Germany	2,472,896	2,945	126,785	151	71,711	85	83,963,843
Greece	197,279	1,899	21,157	204	6,597	64	10,388,744
Hungary	439,900	4,561	98,361	1,020	15,324	159	9,643,837
Ireland	221,189	4,446	193,468	3,889	4,357	88	4,974,683
Italy	2,976,274	4,927	437,421	724	98,635	163	60,401,999
Latvia	88,022	4,702	9,233	493	1,654	88	1,872,109
Lithuania	200,349	7,430	10,859	403	3,281	122	2,696,596
Luxembourg	55,902	8,834	3,074	486	643	102	632,773
Malta	23,226	5,251	3,000	678	321	73	442,333
Netherlands	1,101,430	6,418	-	-	15,697	92	17,160,343
Poland	1,735,406	4,589	249,567	660	44,360	117	37,818,722
Portugal	806,626	7,926	64,797	637	16,430	161	10,176,690
Romania	812,318	4,242	44,953	235	20,586	108	19,151,141
Slovakia	314,359	5,756	51,570	944	7,489	137	5,461,420
Slovenia	192,266	9,247	10,751	517	3,874	186	2,079,130
Spain	3,136,321	6,706	343,770	735	70,247	150	46,766,954
Sweden	675,292	6,659	-	-	12,964	128	10,141,493

a. Active case counts were not available for Netherlands and Sweden; therefore, those two countries are excluded from the overall prevalence calculations for EU-27 and EU-27 + UK.

The reported numbers refer only to cases that have been tested and confirmed to be carrying the virus. There are large geographic variations in the proportion of the population tested as well as in the quality of reporting across countries. People who carry the virus but remain

asymptomatic are less likely to be tested and therefore mild cases are likely underreported. The numbers should therefore be interpreted with caution.[18]

Prevalence:

The prevalence of SARS-CoV-2 infection is defined as active cases per 100,000 people including confirmed cases in people who have not recovered or died. On 03 March 2021, the overall prevalence for the EU and UK (though not available for Sweden and the Netherlands) was 1,398 active cases per 100,000,[15] compared to 51 per 100,000 on 28 July 2020.[16] The range of reported prevalence was 81 to 6,019 per 100,000: Croatia, Denmark, and Germany reported the lowest prevalence while Belgium, France and Ireland reported the highest (Table 32).

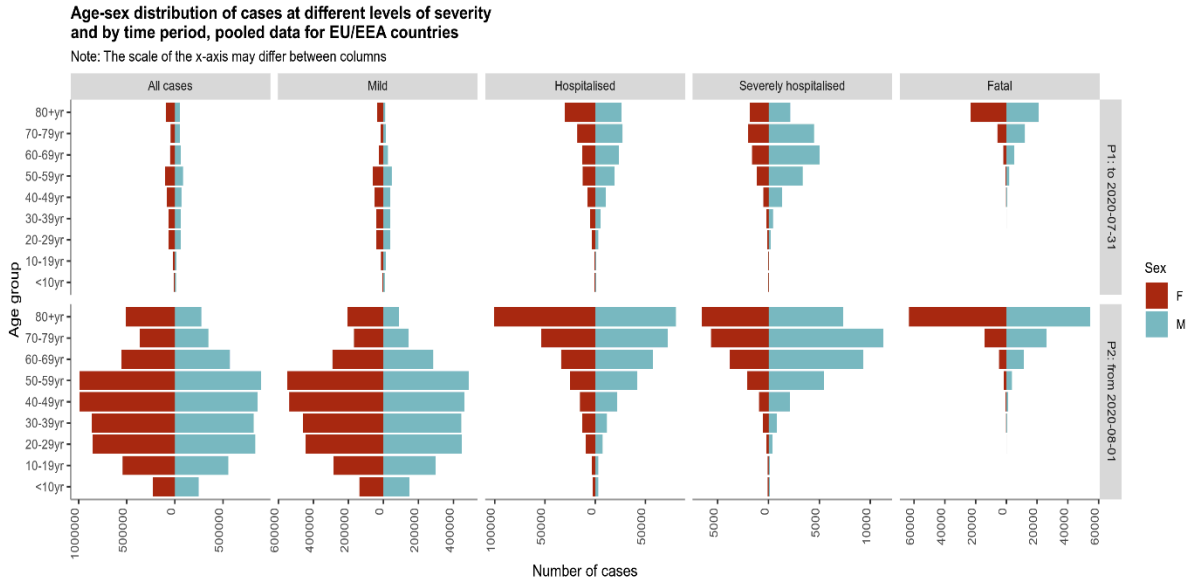
In the US, the prevalence on 03 March 2021 was nearly twice as high as the combined EU+UK estimates, with 2,685 active cases per 100,000.[15] The prevalence in the US was 653 per 100,000 on 28 July 2020.[16]

Demographics of the population in the proposed indication and risk factors for the disease:

Since the beginning of the pandemic, the ECDC has continuously collected COVID-19 information from all countries who are members of EU/EEA and the UK. In the ECDC's TESSy database, COVID-19 case-based data, including age and gender, are available for over 80% of the official number of cases reported by ECDC epidemic intelligence,[19] enabling estimates of age and gender distribution representative of the European population. TESSy data on age and sex distributions by severity of symptoms as posted on 04 March 2021 are shown in Figure 1.[20]

The top half of the figure represents data ending on 31 July 2020 and the bottom half presents data from 01 August 2020 to 04 March 2021 (Figure 1). In general, the age-sex patterns before 01 August 2020 have remained the same since then. The gender distribution of persons testing positive for SARS-CoV-2 in the European population is similar for most age groups. Cases reported in TESSy have been older than the general population throughout the pandemic, with few cases observed in people aged younger than 20 years. This likely reflects the age distribution of people who met the requirements for being tested and is unlikely to reflect the actual distribution of infections in the population. Those with severe outcomes (hospitalized, severely hospitalized, or fatal) have been disproportionately older and male compared to COVID-19 cases overall. While age-sex patterns have remained consistent throughout the pandemic, a notable difference between the periods before and since 01 August 2020 is that the absolute numbers of cases have increased dramatically in the latter period compared to the earlier one.

Figure 1. Age-Sex distribution of COVID-19 Cases as Different Levels of Severity, EU/EEA and UK. Case-based Data from TESSy produced on 04 March 2021[a]



Note: "mild"= a case that has not been reported as hospitalized or a case that resulted in death.

a. Data from ECDC. COVID-19 Surveillance report. Week 8, 2021. 4 March 2021. "2.2 Age-sex pyramids" Accessed 6 March 2021[20]

US distributions of COVID cases and deaths by age, sex, and race, as well as the cross-tabulation of age and sex, are shown in Table 33.[21] Those under age 50 account for 65% of cases but less than 5% of deaths. For ages 18-74, males account for less than half of cases but over 60% of deaths.

Table 33. Distributions of Cases (n=21,895,936) and Deaths (n=382,009) by Age, Sex, Race, and Cross-Tabulated Age and Sex – United States as of 08 March 2021[21,a]

Event	Age Group	Age %	Sex	Sex %	Race[b]	Race %	Age Group	Age x Sex %	
								Males	Females
Cases	**0-4**	2	**Males**	47.8	**H/L**	20.7	**0-4**	51.7	48.3
	5-17	9.5	**Females**	52.2	**AI/AN**	1.2	**5-17**	49.8	50.2
	18-29	22.4			**Asian**	3.6	**18-29**	47.1	52.9
	30-39	16.3			**Black**	12.2	**30-39**	48.2	51.8
	40-49	14.9			**NH/PI**	0.4	**40-49**	47.7	52.3
	50-64	20.5			**White**	56	**50-64**	48.5	51.5
	65-74	7.8			**M/O**	6	**65-74**	49	51
	75-84	4.1					**75-84**	45.7	54.3
	85+	2.4					**85+**	33.9	66.1
Deaths	**0-4**	<0.1	**Males**	54.3	**H/L**	12.2	**0-4**	47.6	52.4
	5-17	0.1	**Females**	45.7	**AI/AN**	1	**5-17**	57.7	42.3
	18-29	0.5			**Asian**	4.3	**18-29**	63	37
	30-39	1.1			**Black**	14.7	**30-39**	66	34
	40-49	2.8			**NH/PI**	0.2	**40-49**	66.5	33.5

Table 33. Distributions of Cases (n=21,895,936) and Deaths (n=382,009) by Age, Sex, Race, and Cross-Tabulated Age and Sex – United States as of 08 March 2021[21,a]

Event	Age Group	Age %	Sex	Sex %	Race[b]	Race %	Age Group	Age x Sex %	
								Males	Females
	50-64	14.5			**White**	63.1	**50-64**	65	35
	65-74	21.3			**M/O**	4.4	**65-74**	61.4	38.6
	75-84	27.7					**75-84**	55.8	44.2
	85+	32.1					**85+**	41.8	58.2

a. Percentage of missing demographic data varied by types of event and demographic.
b. Except for Hispanics/Latinos, all categories refer to non-Hispanics
Abbreviations: AI/AN=American Indian/Alaska Native, H/L=Hispanic/Latino, M/O=Multiple/Other, NH/PI=Native Hawaiian/Other Pacific Islander

In general, disease has been much less severe among ages 0-24 compared to ages ≥25 years, with 2.5% hospitalized, 0.8% admitted to an intensive care unit, and <0.1% dying among ages 0-24, versus 16.6% hospitalized, 8.6% intensive care, and 5% dying among ages ≥25 years.[22] Among hospitalized cases with COVID-19 in the US, approximately 90% are over 40 years old, and between 58% to 66% are at least 60 years old.[23] The majority (approximately 60%) of COVID-19 patients admitted to hospitals in the US have been male.[23,24,25,26,27]

African American COVID-19 patients have been reported to have an increased risk of hospitalization[24,28] and mortality,[29] compared to white patients in the United States. A CDC report examined demographic trends among US COVID-19 deaths from May to August of 2020.[30] During the observation period, the percentage of US COVID-19 deaths that were Hispanic increased from 16.3% in May to 26.4% in August, the only racial or ethnic group among whom the percentage of deaths increased during that time. In terms of setting, 64.3% of deaths occurred in inpatient hospitals and 21.5% in nursing homes or long-term care facilities.

As of 08 March 2021, the CDC estimated that the total number of *excess* deaths (as opposed to overall deaths in the preceding paragraph) across the US from 01 February 2020 to the present from all causes (COVID-19 and otherwise) ranged from 509,890-624,307.[31] A CDC report examining US excess deaths associated with race and age, restricted to the period 26 January 2020 to 03 October 2020, estimated that 66% of US excess deaths during that period were attributable to COVID-19.[32] By age, the largest increase in deaths compared to average expected deaths occurred among adults aged 25-44 (26.5% increase). By race, increases in deaths compared to expectation were largest among Hispanics (53.6% increase), Asian Americans (36.6% increase), African Americans (32.9% increase), and Native Americans and Native Alaskans (28.9% increase), all compared to an excess 11.9% deaths among non-Hispanic whites.

Risk Factors

While anyone can become infected with SARS-CoV-2, symptoms of COVID-19 disease can range from very mild (or no symptoms) to severe or fatal. A person's risk of initial infection

increases through spending time in close physical proximity to others, especially in indoor spaces with poor ventilation.[33] People living in long-term care facilities or high-density apartment homes, or working in occupations with close proximity to others (e.g. healthcare, transportation), have a higher risk of infection.[33,34,35] According to the CDC, people ages 18-29 have the highest risk of initial infection, while children age 4 and under have the lowest rate (Table 34).[36] Risk of infection is also higher among some ethnic minority groups.[37,38]

Table 34. Risk for COVID-19 Infection, Hospitalization, and Death by Age Group [36] and by Race/Ethnicity [37]

	Rate ratios		
Age Group (years)	**Cases**	**Hospitalization**	**Death**
0-4	<1	2	2
5-17 [a]	1	1	1
18-29	3	7	15
30-39	2	10	45
40-49	2	15	130
50-64	2	25	400
65-74	2	35	1100
75-84	2	55	2800
85+	2	80	7900
Race/Ethnicity			
Non-Hispanic White [b]	1	1	1
American Indian or Alaska Native, non-Hispanic	1.9	3.7	2.4
Asian, non-Hispanic	0.7	1.1	1.0
Black or African American, non-Hispanic	1.1	2.9	1.9
Hispanic or Latino	1.3	3.2	2.3

a. Rate ratios for each age group are relative to the 5—17-year age category.
b. Rate ratios for each race/ethnicity group are relative to the Non-Hispanic White category.

Risk for severe or fatal COVID-19 disease has been shown to increase with older age, male sex, or ethnic minority status.[36,37,38,39,40,41] Risks of hospitalization and death increase dramatically for every 10-year age group above age 17 (Table 34).[36,41] Table 34 also gives estimated rate ratios for COVID-19 hospitalization and death by race/ethnicity relative to white, non-Hispanic persons in the US. The highest risks of hospitalization and death were observed among American Indian or Alaska native persons (RR = 3.7 for hospitalization and 2.4 for death) and Hispanic or Latino persons (RR = 3.2 for hospitalization and 2.3 for death). These differences in risk among ethnic groups may be attributed to differences in underlying factors that are correlated with race/ethnicity including socioeconomic status, access to health care, and occupation-related virus exposure.[37]

Risk of severe or fatal COVID-19 disease is higher among persons who are current or former smokers, have lower socioeconomic status, have no or public insurance, or live in neighborhoods with higher rates of limited English proficiency.[38,40,41,42] The CDC has also recognized other socio-demographic groups who may need to take extra precautions against COVID-19 due to increased risk for severe illness: pregnant women; breastfeeding mothers; people with disabilities or developmental/behavioral disorders; people living in rural

communities, nursing homes, long-term care facilities, or prisons; people experiencing homelessness; and newly resettled refugee populations.[43]

Risk for severe or fatal COVID-19 disease also increases with the presence of chronic medical conditions, including obesity, respiratory diseases (e.g., COPD or asthma), cardiovascular disease, diabetes, cancer, liver disease, neurological diseases (e.g., stroke or dementia), chronic kidney disease, sickle cell disease, autoimmune conditions and immunosuppression, or higher scores on the WHO Clinical Progression Scale and Charlson Comorbidity Index.[38,39,40,41,42] Table 35 shows the estimated hazard ratios of COVID-19 mortality associated with these chronic conditions and socio-demographics from a cohort study of 17 million adults in England.[41]

Table 35. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death[41]

		COVID-19 death Hazard Ratio	
Characteristic	**Category**	**Adjusted for age and sex**	**Fully adjusted**
Age	18-39	0.05 (0.04-0.07)	0.06 (0.04-0.08)
	40-49	0.28 (0.23-0.33)	0.30 (0.25 - 0.36)
	50-59	1.00 (ref)	1.00 (ref)
	60-69	2.79 (2.52-3.10)	2.40 (2.16-2.66)
	70-79	8.62 (7.84-9.46)	6.07 (5.51-6.69)
	80+	38.29 (35.02-41.87)	20.60 (18.70-22.68)
Sex	Female	1.00 (ref)	1.00 (ref)
	Male	1.78 (1.71-1.85)	1.59 (1.53-1.65)
BMI (kg/m^2)	Not obese	1.00 (ref)	1.00 (ref)
	30-34.9 (obese class I)	1.23 (1.17–1.30)	1.05 (1.00–1.11)
	35-39.9 (obese class II)	1.81 (1.68–1.95)	1.40 (1.30–1.52)
	40+ (obese class III)	2.66 (2.39–2.95)	1.92 (1.72–2.13)
Smoking	Never	1.00 (ref)	1.00 (ref)
	Former	1.43 (1.37–1.49)	1.19 (1.14–1.24)
	Current	1.14 (1.05–1.23)	0.89 (0.82–0.97)
Ethnicity[a]	White	1.00 (ref)	1.00 (ref)
	Mixed	1.62 (1.26–2.08)	1.43 (1.11–1.84)
	South Asian	1.69 (1.54–1.84)	1.45 (1.32–1.58)
	Black	1.88 (1.65–2.14)	1.48 (1.29–1.69)
	Other	1.37 (1.13–1.65)	1.33 (1.10–1.61)
IMD quintile[e]	1 (least deprived)	1.00 (ref)	1.00 (ref)
	2	1.16 (1.08-1.23)	1.12 (1.05–1.19)
	3	1.31 (1.23–1.40)	1.22 (1.15–1.30)
	4	1.69 (1.59–1.79)	1.51 (1.42–1.61)
	5 (most deprived)	2.11 (1.98–2.25)	1.79 (1.68–1.91)
Blood pressure	Normal	1.00 (ref)	1.00 (ref)
	High BP or diagnosed hypertension	1.09 (1.05–1.14)	0.89 (0.85–0.93)
Respiratory disease excluding asthma		1.95 (1.86–2.04)	1.63 (1.55–1.71)
Asthma[b] (vs. none)	With no recent OCS use	1.13 (1.07–1.20)	0.99 (0.93–1.05)
	With recent OCS use	1.55 (1.39–1.73)	1.13 (1.01–1.26)

Table 35. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death[41]

		COVID-19 death Hazard Ratio	
Characteristic	**Category**	**Adjusted for age and sex**	**Fully adjusted**
Chronic heart disease		1.57 (1.51–1.64)	1.17 (1.12–1.22)
Diabetes[c] (vs. none)	With HbA1c < 58 mmol/mol	1.58 (1.51–1.66)	1.31 (1.24–1.37)
	With HbA1c ≥ 58 mmol/mol	2.61 (2.46–2.77)	1.95 (1.83–2.08)
	With no recent HbA1c measure	2.27 (2.06–2.50)	1.90 (1.72–2.09)
Cancer (non-hematological, vs. none)	Diagnosed <1 year ago	1.81 (1.58–2.07)	1.72 (1.50–1.96)
	Diagnosed 1-4.9 years ago	1.20 (1.10–1.32)	1.15 (1.05–1.27)
	Diagnosed ≥ 5 years ago	0.99 (0.93–1.06)	0.96 (0.91–1.03)
Hematological malignancy (vs. none)	Diagnosed <1 year ago	3.02 (2.24–4.08)	2.80 (2.08–3.78)
	Diagnosed 1-4.9 years ago	2.56 (2.14–3.06)	2.46 (2.06–2.95)
	Diagnosed ≥ 5 years ago	1.70 (1.46–1.98)	1.61 (1.39–1.87)
Reduced kidney function[d] (vs. none)	eGFR 30-60	1.56 (1.49–1.63)	1.33 (1.28–1.40)
	eGFR < 30	3.48 (3.23–3.75)	2.52 (2.33–2.72)
Liver disease		2.39 (2.06–2.77)	1.75 (1.51–2.03)
Stroke or dementia		2.57 (2.46–2.70)	2.16 (2.06–2.27)
Other neurological disease		3.08 (2.85–3.33)	2.58 (2.38–2.79)
Organ transplant		6.00 (4.73–7.61)	3.53 (2.77–4.49)
Asplenia		1.62 (1.19–2.21)	1.34 (0.98–1.83)
Rheumatoid arthritis, lupus, or psoriasis		1.30 (1.21–1.38)	1.19 (1.11–1.27)
Other immunosuppressive condition		2.75 (2.10–3.62)	2.21 (1.68–2.90)

a. Ethnicity hazard ratios were estimated from a model restricted to those with recorded ethnicity.
b. For OCS use, 'recent' refers to during the year before baseline.
c. Classification by HbA1c is based on measurements within 15 months of baseline.
d. eGFR is measured in ml min−1 per 1.73 m^2 and taken from the most recent serum creatinine measurement.
e. Index of Multiple Deprivation
Models were adjusted for age using a four-knot cubic spline for age, except for estimation of age-group hazard ratios. Ref, reference group; 95% CI, 95% confidence interval.

The main existing treatment options:

Through 28 February 2021, other COVID-19 vaccines were authorized and recommended for use in the United States including vaccines from Moderna (NCT04470427), and Johnson & Johnson/Janssen (NCT04505722). Others may subsequently be approved.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Symptoms of COVID-19

The clinical manifestations of COVID-19 vary widely, from asymptomatic infection in 17-20%,[44,45] to critical illness and death. The most common symptoms of COVID-19 are fever, cough, and shortness of breath (Table 36).[46]

Table 36. Signs and symptoms among 291 pediatric (age <18 years) and 10,944 adult (age 18–64 years) patients[a] with laboratory confirmed COVID-19 — United States, 12 February– 2April 2020[46]

	No. (%) with sign/symptom	
Sign/Symptom	**Pediatric**	**Adult**
Fever, cough, or shortness of breath[b]	213 (73)	10,167 (93)
Fever[d]	163 (56)	7,794 (71)
Cough	158 (54)	8,775 (80)
Shortness of breath	39 (13)	4,674 (43)
Myalgia	66 (23)	6,713 (61)
Runny nose[c]	21 (7.2)	757 (6.9)
Sore throat	71 (24)	3,795 (35)
Headache	81 (28)	6,335 (58)
Nausea/Vomiting	31 (11)	1,746 (16)
Abdominal pain[d]	17 (5.8)	1,329 (12)
Diarrhea	37 (13)	3,353 (31)

a. Cases were included in the denominator if they had a known symptom status for fever, cough, shortness of breath, nausea/vomiting, and diarrhea. Total number of patients by age group: <18 years (N = 2,572), 18–64 years (N = 113,985).
b. Includes all cases with one or more of these symptoms.
c. Runny nose and abdominal pain were less frequently completed than other symptoms; therefore, percentages with these symptoms are likely underestimates.
d. Patients were included if they had information for either measured or subjective fever variables and were considered to have a fever if "yes" was indicated for either variable.

Progression and Timeline of Mild to Moderate Disease

Mild to moderate disease is defined as the absence of viral pneumonia and hypoxia. For those who develop symptoms, the incubation period is usually 4 to 5 days, with 97.5% experiencing symptoms within 11 days of exposure.[47,48] Those with mild COVID-19 recover at home with supportive care and guidance to self-isolate. Those with moderate disease are monitored at home and are sometimes recommended to be hospitalized if conditions worsen.[48] Data on rates of re-infection are limited but variants that are not neutralized by immune antisera, such as the recent South African variant, may lead to increased risk of re-infection in the future.[47]

Progression and Timeline of Severe Disease Requiring Hospitalization

Those with severe disease will require hospitalization to manage their illness. Based on data that have been systematically collected for the US by the CDC between 01 August 2020 and 02 March 2021, there were 1,814,606 new hospital admissions for patients with confirmed COVID-19 in the US.[49] For the week ending 28 February 2021, 10 patients per 100,000 population were hospitalized due to COVID-19 in 22 countries of the EU/EEA with available data.[50]

The most common symptoms in patients are fever (42-80%), shortness of breath (35-71%), fatigue (33-62%), cough (77-84%), chills (63%), myalgias (63%), headache (59%), and diarrhea (33%).[51,52,53,54] Approximately 17% to 40% of those hospitalized with COVID-19

experience severe symptoms necessitating intensive care.[23,28,51] More than 75% of patients hospitalized with COVID-19 require supplemental- oxygen.[55]

Studies early in the pandemic demonstrated that time from onset of illness to ARDS was 8-12 -days and time from onset of illness to ICU admission was 9.5–12 days.[47] In 17 countries of the EU/EEA with available data, 1.8 patients per 100,000 population were in the ICU due to COVID-19 for the week ending 28 February 2021.[50] A recent meta-analysis found that, of patients <19 years of age, 11% went to the ICU, non-invasive ventilation was administered among 12%, and 4% required mechanical ventilation.[45]

Mortality

As of 07 March 2021, there were 522,973 deaths reported in the US for all age groups among 28,771,749 cases (1.8% of cases).[49] As of 28 February 2021 there were 547,267 deaths reported for all age groups in the EU/EEA among 22,527,370 cases (2.4% of cases).[56] As of 7 March 2021, the UK has seen 124,736 deaths from COVID-19 in all age groups among 4,231,166 cases (2.9% of cases).[57] According to a recent meta-analysis of pediatric studies published through October 2020, the mortality for patients <19 years of age is 2%.[45]

Mortality data are also presented from Worldometer, an independent organization that publishes current, reliable COVID-19 statistics online.[17] The mortality of SARS-CoV-2 infection is defined as the cumulative number of deaths among detected cases.

As of 03 March 2021, the overall SARS-CoV-2 mortality for the EU + UK was 677,146 deaths, or 132 per 100,000 people. Reported mortality among EU countries and the UK ranged from 14 to 195 deaths per 100,000 (Table 32). Finland and Cyprus reported the lowest mortality; Czech Republic, Belgium and Slovenia reported the highest.[15]

In the US, as of 03 March 2021, the mortality was 531,652 deaths (160 per 100,000 people). Mortality in the US was similar to that of EU countries Hungary, Portugal, and Italy. [15]

Overall reported mortality among hospitalized COVID-19 patients varies from 12.8% to 26% in the EU and UK. [28,30,58,59] Mortality rates are declining over time, presumably due to an improved understanding of COVID-19 and its management.[58,60]

Complications of COVID-19 and Long-COVID

Complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney, and coagulation system.[23,25,54] Based on a meta-analysis of 42 studies, the risk of thromboembolism was 21% overall and 31% in the ICU, with the pooled odds of mortality being 74% higher among those who experienced thromboembolism compared to those who did not.[61]

COVID-19 symptoms can persist weeks or months beyond the acute infection.[62,63] The NICE guideline scope published on 30 October 2020 defined “Long COVID” signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more and for which signs and symptoms are not explained by an alternative diagnosis).[64]

A meta analysis of 31 studies among patients between 18 to 49 years of age found that COVID-19 symptoms were experienced for 14 days to 3 months post-infection, including persistent fatigue (39–73%), breathlessness (39–74%), decrease in quality of life (44–69%), impaired pulmonary function, abnormal CT findings including pulmonary fibrosis (39–83%), evidence of peri-/perimyo-/myocarditis (3–26%), changes in microstructural and functional brain integrity with persistent neurological symptoms (55%), increased incidence of psychiatric diagnoses (5.8% versus 2.5–3.4% in controls), and incomplete recovery of olfactory and gustatory dysfunction (33–36%).[65] Children who are infected with COVID-19 are at risk of subsequent multisystem inflammatory syndrome (MIS-C) and often develop a rash following resolution of COVID-19.[66,67,45]

Important co-morbidities:

Important comorbidities in hospitalized COVID-19 patients include hypertension, diabetes, obesity, cardiovascular disease, chronic pulmonary disease or asthma, chronic kidney disease, cancer, and chronic liver disease.[24,25,26,51,54] Prevalence of these conditions have been reported to be lower in mild cases and higher among fatal cases, as shown as shown for European countries in Table 37 below.

Table 37. Preconditions among COVID-19 Patients in EU/EEA and UK, by Severity of Disease. Case-based Data from TESSy Produced 04 March 2021

	EU/EEA, produced on 04 March 2021			
	Mild	**Hosp**	**Severe**	**Fatal**
Total N	1,155,969	214,784	35,468	67,011
Asplenia (%)	0	0	0	0
Asthma (%)	0.5	1.6	1.7	1.6
Cancer, malignancy (%)	2.1	7.2	9.7	9.3
Cardiac disorder, excluding hypertension (%)	6.2	18.4	20.7	24.7
Chronic lung disease, excluding asthma (%)	1.8	4.7	5.3	5.3
Current smoking (%)	0.9	0.3	0.4	0.1
Diabetes (%)	3.3	13.9	18.9	15.6
Haematological disorders (%)	0	0.3	0.1	0.2
HIV/other immune deficiency (%)	0.1	0.9	1	0.8
Hypertension (%)	0.7	3.9	4.4	6.3
Kidney-related condition, renal disease (%)	0.3	2.3	2.2	3.7
Liver-related condition, liver disease (%)	0.2	0.7	0.7	0.6
Neuromuscular disorder, chronic neurological (%)	0.6	2.4	1.6	4.2
Obesity (%)	0.2	0.2	0.4	0.2
Other endocrine disorder, excluding diabetes (%)	0.4	0.2	0.1	0.1
Rheumatic diseases including arthritis (%)	0	0	0	0
Tuberculosis (%)	0	0	0	0
None (%)	82.5	42.8	32.7	27.3

Abbreviation: Hosp = Hospitalized

Table 38 below summarizes comorbidities among US COVID-19 patients in a retrospective cohort study conducted among 629,953 individuals tested for COVID-19 in a large health system in the US Northwest between 01 March and 31 December 2020.[38] The most common comorbidities were similar in the full cohort and among those who tested positive: obesity, hypertension, diabetes, and asthma. Among those hospitalized for COVID-19, a large

number of comorbidities had elevated prevalence compared to the full cohort and those who tested positive: obesity, hypertension, diabetes, kidney disease, congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease.

Table 38. Comorbidities in individuals tested for COVID-19 in the Providence St. Joseph Health System – States of California, Oregon, and Washington, 01 March–31 December 2020[38]

Comorbidity	Tested (N= 629,953) %	Positive (N= 54,645) %	Hospitalized (N= 8,536) %
Hypertension	23.3	19.8	40.2
Diabetes	9.4	10.9	28.3
Weight			
Underweight	2.1	1.7	3.1
Normal	29.0	23.9	24.3
Overweight	31.7	32.6	30.3
Class 1 Obesity	19.8	22.3	21.2
Class 2 Obesity	9.6	11.1	10.9
Class 3 Obesity	7.7	8.6	10.3
Asthma	6.5	5.3	6.7
Chronic Obstructive Pulmonary Disease	4.0	2.6	8.3
Coronary Artery Disease	5.5	3.6	9.7
Myocardial Infarction	2.2	1.6	5.5
Congestive Heart Failure	5.3	3.9	13.2
Kidney Disease	5.6	5.3	17.2
Liver Disease	3.1	2.5	4.0
Cancer	6.1	3.0	6.3

2.1.2.f. Pharmacological Class Effects

There are 2 vaccines (including BNT162b2) with a mRNA platform authorized for emergency use in multiple US jurisdictions since 11 December 2020. Theoretical concerns in mRNA vaccines have included the risk of the presence of naked extracellular RNA in the body which may lead to edema or coagulation and concerns about aberrant immune responses to the RNA or lipid particles. The immunogenicity and efficacy data from study C4591001 are indicative of the vaccine delivery system's success in transfecting the RNA into the appropriate target cells to stimulate an immune response. The RNA itself cannot integrate into the DNA genome.[68,69] The probability of any sequences from the vaccine RNA being integrated into the human genome by a reverse transcription mediated mechanism is considered remote, no higher than the probability of host RNA sequences being re-inserted into the genome, especially given the small quantity of RNA in the vaccine, the barriers to transfected RNA reaching the nucleus, the non-replicating nature of the vaccine RNA, the limited stability of RNA in a cellular context, and the expected targeting of transfected cells for elimination by T cells elicited by the vaccine antigen expressed from the RNA.

3. PHARMACOVIGILANCE PLAN

3.1. Structure of the Pharmacovigilance Plan

3.1.1. Summary of Ongoing Safety Concerns

Table 39. Ongoing Safety Concerns

Important Identified Risks	Anaphylaxis
	Myocarditis and Pericarditis
Important Potential Risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use in pregnancy and lactation
	Vaccine effectiveness
	Use in pediatric individuals <12 years of age

3.1.2. Routine Pharmacovigilance Practices

- Routine pharmacovigilance activities is a critical component of activities relating to the detection, assessment, understanding and prevention of risks. The objective of routine pharmacovigilance is to have processes in place to assure the ongoing and timely collection, processing, follow-up, and analysis of individual AE reports globally, following global safety Standard Operating Procedures and regulatory guidance.

- Pfizer, on behalf of the marketing authorization applicant (MAA), monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant information is conveyed in a timely manner to regulatory authorities and other interested parties as appropriate and in accordance with international principles and prevailing regulations.

- Pfizer, on behalf of the MAA, conducts scientific data gathering activities for the detection and evaluation of AEs in order to ensure safety monitoring, which is commensurate with product characteristics.

- Signal detection activities include periodic literature review for the life cycle of the product. This includes reviewing the medical literature for individual case reports that should be entered into the safety database as well as periodic aggregate literature review for broader signal detection.

- Safety signal evaluation requires the collection, analysis and assessment of information to evaluate whether there is a potential causal association between an event and the administration of the product and includes subsequent qualitative or quantitative characterization of the relevant safety risk to determine appropriate pharmacovigilance and risk mitigation actions.

- Routine pharmacovigilance activities will include the use of DCAs. They are intended to facilitate the capture of clinical details about:
  - the nature and severity of COVID-19 illness in individuals who have received the COVID-19 vaccine and is anticipated to provide insight into potential cases of vaccine lack of effect or VAED.
  - potential anaphylactic reactions in individuals who have received the COVID-19 vaccine.
- A web-based AE reporting portal will be available for vaccine providers and recipients, to assist with anticipated high volume of reports (based on expected large target population). The portal will capture key adverse event data in the initial interaction and will provide automated intake into the Pfizer safety database via E2B for safety review.
- At the country level, the Drug Safety Unit performs routine pharmacovigilance activities including the collection of AEs from various sources and the reporting of AEs to the regulatory authority as per local regulatory guidelines.

3.1.3. Action Plan for Safety Issues

Action Plan for Important Identified Risks

Table 40. Action Plan for Important Identified Risk "Myocarditis and Pericarditis"

Actions proposed	• C4591009: A non-interventional post-approval safety study of the Pfizer--BioNTech COVID-19 mRNA vaccine in the United States. • C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 vaccine in the US Department of Defense population following Emergency Use Authorization. • 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.
Objective of proposed actions	• C4591009: To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System. • C4591011: To assess whether individuals in the US DoD Military Health System (MHS) experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the Pfizer-BioNTech COVID-19 Vaccine. • C4591012: To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the Pfizer-BioNTech COVID-19 Vaccine.
Rationale for proposed actions	• C4591009: Robust surveillance is needed to ensure comprehensive understanding of real-world safety of the Pfizer-BioNTech COVID-19 Vaccine in the general US population and in subcohorts of interest, including pregnant women, immunocompromised individuals and persons with a prior history of COVID-19 infection. • C4591011 and C4591012: Robust surveillance is needed to ensure comprehensive understanding of real-world safety. This surveillance strategy consists of complementary approaches to ensure timely signal identification and evaluation in populations who have received the Pfizer-BioNTech COVID-19 Vaccine under an Emergency Use Authorization (EUA).
Monitoring by the sponsor for safety issue and proposed actions	• C4591009: Post-approval observational studies using real-world data are needed to assess the association between Pfizer-BioNTech COVID-19 Vaccine and safety events of interest, among persons administered the vaccine in both the overall US population and in populations of interest (e.g., pregnant women, the immunocompromised and persons with a prior history of COVID-19 infection). This observational study will capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the Pfizer-BioNTech COVID-19 Vaccine since its availability under an EUA using electronic health records and claims data from data partners participating in the Sentinel System. This study, will capture hospitalizations, deaths and serious safety events of interest, including myocarditis and pericarditis, as well as selected pregnancy-related and birth outcomes. • C4591011 and C4591012: 1. The collection of safety data in vaccine recipients is critical to our understanding of the vaccine safety profile and to enable safety signal

Table 40. Action Plan for Important Identified Risk "Myocarditis and Pericarditis"

	detection and, if needed, further risk mitigation during the EUA. In addition to the collection and monitoring of AEs reported voluntarily by healthcare professionals providing the vaccine and by individuals receiving the vaccine, active surveillance studies of the Pfizer-BioNTech COVID-19 Vaccine under EUA are also planned. 2. Active surveillance of large numbers of individuals vaccinated with the Pfizer-BioNTech COVID-19 Vaccine is necessary to confirm the safety profile demonstrated in the clinical study in a broader population under real-world conditions. Pfizer-BioNTech is conducting active surveillance studies of individuals vaccinated with the Pfizer--BioNTech COVID-19 Vaccine under an EUA in populations prioritized in the early stages of the EUA, e.g., active military and elderly, as described in the study protocols C4591011 (study planned) and C4591012 (study ongoing) submitted to FDA on 29 January 2021. The study period is/will be approximately 30 months following availability of vaccine under EUA. The studies capture hospitalizations, deaths and serious safety events of interest, including myocarditis and pericarditis.

Milestones for evaluation and reporting	• C4591009:
	  • Protocol submission: 31 August 2021
	  • Monitoring report submission: 31 October 2022
	  • Interim Analysis submission: 31 October 2023
	  • Final study report submission: 31 October 2025.
	• C4591011:
	  • Interim study reports[a] will be submitted on the following dates based on data collected post-EUA in target populations:
	  – 31 December 2021
	  – 30 June 2022
	  – 31 December 2022
	  • Final study reports submission: 31 December 2023.
	• C4591012
	  • Interim study reports will be submitted on the following dates based on data collected post-EUA in target populations:
	  – 30 June 2021
	  – 31 December 2021
	  – 30 June 2022
	  – 31 December 2022
	  • Final study reports submission: 31 December 2023.

a. FDA was informed (Response to FDA 12 May 2021 - Information Request Regarding Active Surveillance Studies) that the first milestone (Interim Report submission due 30 June 2021) is delayed due to a change in study collaboration; therefore it has been removed from this table.

Table 41. Action Plan for Important Identified Risk "Anaphylaxis"

Actions proposed	• Communication of this 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*). • 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 RNA vaccine candidates against COVID-19 in healthy individuals. • C4591009: A non-interventional post-approval safety study of the Pfizer--BioNTech COVID-19 mRNA vaccine in the United States. • C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 vaccine in the US Department of Defense population following Emergency Use Authorization. • 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.
Objective of proposed actions	• Labelling communicates the risk of anaphylaxis. • C4591001: To evaluate the safety, tolerability, immunogenicity, and efficacy of BNT162b2. Further, an unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of VAED/VAERD. Surveillance is planned for 2 years following Dose 2. • C4591009: To assess the occurrence of safety events of interest in the general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System. • C4591011: To assess whether individuals in the US DoD Military Health System (MHS) experience increased risk of safety events of interest, following receipt of the BNT162b2. • C4591012: To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following receipt of the BNT162b2.
Rationale for proposed actions	• Labeling communicates to health care provider the risk of anaphylaxis. • C4591001: Long-term monitoring throughout the clinical study for up to 2 years to assess the risk for vaccine-associated enhanced disease. • C4591009: Robust surveillance is needed to ensure comprehensive understanding of real-world safety of the BNT162b2 in the general US population and in subcohorts of interest, including pregnant women, immunocompromised individuals and persons with a prior history of COVID-19 infection. • C4591011 and C4591012: Robust surveillance is needed to ensure comprehensive understanding of real-world safety. This surveillance strategy consists of complementary approaches to ensure timely signal identification and evaluation in populations expected to receive the BNT162b2 under an Emergency Use Authorization (EUA).
Monitoring by the sponsor for safety issue and proposed actions	• C4591001: Safety evaluations will include AESI, including anaphylaxis; these will be collected systemically and monitored throughout the Phase 3 study. • C4591009: Post-approval observational studies using real-world data are needed to assess the association between BNT162b2 and safety events of

Table 41. Action Plan for Important Identified Risk "Anaphylaxis"

	interest, among persons administered the vaccine in both the overall US population and in populations of interest (e.g., pregnant women, the immunocompromised and persons with a prior history of COVID-19 infection). This observational study will capture safety events (based on AESI) including anaphylaxis, in individuals of any age who received the BNT162b2 since its availability under an EUA using electronic health records and claims data from data partners participating in the Sentinel System. This study, will capture hospitalizations, deaths and serious safety events of interest, including anaphylaxis, as well as selected pregnancy-related and birth outcomes. • C4591011 and C4591012: 1. The collection of safety data in vaccine recipients is critical to our understanding of the vaccine safety profile and to enable safety signal detection and, if needed, further risk mitigation during the EUA. In addition to the collection and monitoring of AEs reported voluntarily by healthcare professionals providing the vaccine and by individuals receiving the vaccine, active surveillance studies of the BNT162b2 under EUA are also planned. 2. Active surveillance of large numbers of individuals vaccinated with the BNT162b2 is necessary to confirm the safety profile demonstrated in the clinical study in a broader population under real-world conditions. Pfizer-BioNTech plans to conduct active surveillance studies of individuals vaccinated with the BNT162b2 under an EUA in populations prioritized in the early stages of the EUA, e.g., active military and elderly, as described in the study protocols C4591011 and C4591012 submitted to FDA on 29 January 2021. The study period will be approximately 30 months following availability of vaccine under EUA. The studies will capture hospitalizations, deaths and serious safety events of interest, including anaphylaxis.
Milestones for evaluation and reporting	• C4591001 (ongoing Study): • CSR submission upon regulatory request: at any time • CSR submission 6 months post Dose 2: 31 May 2021 • Final CSR submission with supplemental follow-up: 31 August 2023. • C4591009: • Protocol submission: 31 August 2021 • Monitoring report submission: 31 October 2022 • Interim Analysis submission: 31 October 2023 • Final study report submission: 31 October 2025. • C4591011 • Interim study reports[a] will be submitted on the following dates based on data collected post-EUA in target populations: – 31 December 2021 – 30 June 2022 – 31 December 2022 • Final study reports submission: 31 December 2023. • C4591012 • Interim study reports will be submitted on the following dates based on data collected post-EUA in target populations:

Table 41. Action Plan for Important Identified Risk "Anaphylaxis"

	– 30 June 2021 – 31 December 2021 – 30 June 2022 – 31 December 2022 • Final study reports submission: 31 December 2023.

a. FDA was informed (Response to FDA 12 May 2021 - Information Request Regarding Active Surveillance Studies) that the first milestone (Interim Report submission due 30 June 2021) is delayed due to a change in study collaboration;, therefore, it has been removed from in this table.

Action Plan for Important Potential Risks

Table 42. Action Plan for Important Potential Risk "Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)"

Actions proposed	• 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 RNA vaccine candidates against COVID-19 in healthy individuals. • C4591008: HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 Vaccine in US healthcare workers, their families, and their communities. • C4591009: A non-interventional post-approval safety study of the Pfizer--BioNTech COVID-19 mRNA vaccine in the United States. • C4591011: Active safety surveillance of the Pfizer--BioNTech COVID-19 vaccine in the US Department of Defense population following Emergency Use Authorization. • 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.
Objective of proposed actions	• C4591001: to evaluate the safety, tolerability, immunogenicity, and efficacy of BNT162b2. An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of VAED/VAERD. Surveillance is planned for 2 years following Dose 2. • C4591008, C4591009, C4591011, and C4591012: to characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease, among individuals vaccinated with the BNT162b2 since EUA.
Rationale for proposed actions	• C4591001: Robust and long-term monitoring throughout the clinical study for up to 2 years to assess the risk for vaccine-associated enhanced disease. • C4591008, C4591009, C4591011 and C4591012: Robust surveillance is needed to ensure comprehensive understanding of real-world safety. This surveillance strategy consists of complementary approaches to ensure timely signal identification and evaluation in populations expected to receive the vaccine in the early stages of an EUA as well as with broader vaccination roll-out.
Monitoring by the sponsor for safety	• C4591001: Protocol prespecified stopping and alert rules were set for detecting enhanced COVID-19.

Table 42. Action Plan for Important Potential Risk "Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)"

issue and proposed actions Monitoring by the sponsor for safety issue and proposed actions *(Cont'd)*	Participants in all stages of the study will be monitored for COVID-19 illness including severe COVID-19 from Visit 1 onward. Cases will undergo blinded review to identify whether any features of each case appear unusual, in particular greater severity. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. The Data Monitoring Committee, supported by an unblinded medical monitor, will look for adverse imbalances between vaccine and control groups in COVID-19 disease outcomes, in particular for cases of severe COVID-19, that may be a signal for vaccine-associated enhanced disease on an ongoing basis and at interim analyses. Stopping rules were set so that enrollment could be paused in the event of an adverse imbalance. Additional safety evaluations will include AESI that could represent symptoms of severe COVID-19 disease; these will be collected systemically and monitored throughout the Phase 3 study. • C4591008, C4591011, C4591012: The collection of safety data in vaccine recipients is critical to our understanding of the vaccine safety profile and to enable efficient safety signal detection and, if needed, further risk mitigation during the EUA. In addition to the collection and monitoring of AEs reported voluntarily by healthcare professionals providing the vaccine and by individuals receiving the vaccine, active surveillance studies of the BNT162b2 under EUA are also planned. Active surveillance of large numbers of individuals vaccinated with the BNT162b2 is necessary to confirm the safety profile demonstrated in the clinical study in a broader population under real-world conditions. Pfizer-BioNTech plans to conduct active surveillance studies of vaccinated individuals in populations prioritized in the early stages of the EUA, e.g., healthcare workers, active military, and elderly, as described in C4591008 protocol submitted to FDA on 28 January 2021; C4591011 protocol submitted to FDA on 29 January 2021 and C4591012 protocol submitted to FDA on 29 January 2021. The study period will be approximately 30 months following availability of vaccine under EUA. The studies will capture hospitalizations, deaths and serious safety events of interest, including severe COVID-19 (which, if associated with vaccination, may indicate VAED/VAERD). • C4591009: Surveillance of large numbers of individuals vaccinated with the BNT162b2 is necessary to confirm the safety profile demonstrated in the clinical study in a broader population under real-world conditions. This study is intended to capture a broader sample of vaccinated individuals of any age in the general US population using large scale data sources.
Milestones for evaluation and reporting	• C4591001 (ongoing Study): • CSR submission upon regulatory request: at any time • CSR submission 6 months post Dose 2: 31 May 2021 • Final CSR submission with supplemental follow-up: 31 August 2023. • Three observational post-authorization safety studies for EUA (C4591008, C4591011, and C4591012): • C4591008 and C4591012: Interim study reports will be submitted on the following dates based on data collected post-EUA in target populations: o 30 June 2021 o 31 December 2021 o 30 June 2022

Table 42. Action Plan for Important Potential Risk "Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)"

	○ 31 December 2022 • Final study reports submission: 31 December 2023. • C4591011: Interim study reports[a] will be submitted on the following dates based on data collected post-EUA in target populations: ○ 31 December 2021 ○ 30 June 2022 ○ 31 December 2022 • Final study reports submission: 31 December 2023. • C4591009: • Protocol submission: 31 August 2021 • Monitoring report submission: 31 October 2022 • Interim Analysis submission: 31 October 2023 • Final study report submission: 31 October 2025.

a. FDA was informed (Response to FDA 12 May 2021 - Information Request Regarding Active Surveillance Studies) that the first milestone (Interim Report submission due 30 June 2021) is delayed due to a change in study collaboration;, therefore, it has been removed from in this table.

Action Plan for Missing Information

Table 43. Action Plan for Missing Information "Use in Pregnancy and Lactation"

Actions proposed	• 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. • C4591009: A non-interventional post-approval safety study of the Pfizer--BioNTech COVID-19 mRNA vaccine in the United States. • C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the US Department of Defense population following Emergency Use Authorization. • 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)/MotherToBaby Pregnancy Registry.
Objective of proposed actions	• C4591015: To assess safety and immunogenicity of BNT162b2 in pregnant women. In addition, exploratory objectives include: To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic BNT162b2 during pregnancy. To describe the safety of maternal immunization in infants born to breastfeeding maternal participants vaccinated with prophylactic BNT162b2 during pregnancy. • C4591009[a]: To assess whether pregnant women experience increased risk of safety events of interest following receipt of the BNT162b2. • C4591011[a]: To assess whether sub-cohorts of interest, such as pregnant women, in the MHS experience increased risk of safety events of interest following receipt of the BNT162b2.

Table 43. Action Plan for Missing Information "Use in Pregnancy and Lactation"

	• C4591022[a]: To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age.
Rationale for proposed actions	Acquisition of data in an unstudied population with potentially different safety considerations from the time vaccine is available.
Monitoring by the sponsor for safety issue and proposed actions	• C4591015: Monitoring via ongoing clinical study. • C4591009: The collection of safety data in vaccine recipients, including pregnant women, is critical to our understanding of the vaccine safety profile and to enable robust safety signal detection and evaluation and, if needed, further risk mitigation under BLA. • C4591011: 1. The collection of safety data in vaccine recipients is critical to our understanding of the vaccine safety profile and to enable efficient safety signal detection and, if needed, further risk mitigation. Active surveillance studies of the BNT162b2 under EUA are also planned. 2. Active surveillance of large numbers of individuals vaccinated with the BNT162b2 is necessary to confirm the safety profile demonstrated in the clinical study in a broader population under real-world conditions. Pfizer-BioNTech plans to conduct active surveillance studies of individuals vaccinated with the BNT162b2 under an EUA in populations prioritized in the early stages of the EUA, e.g., active military and their family members, as described in C4591011 (protocol submitted to FDA on 29 January 2021). The study period will be approximately 30 months following availability of vaccine under EUA. The study will capture hospitalizations, deaths and serious safety events of interest, including anaphylaxis. • C4591022: This study will monitor rates of pregnancy and infant outcomes in planned and unplanned pregnancies exposed to BNT162b2 using an established pregnancy registry. Women receiving BNT162b2 during pregnancy will be followed from exposure to one-year post-partum. Analyses will be conducted to evaluate if the pregnant women receiving the vaccine during pregnancy experience increased risk of pregnancy and infant outcomes compared with 1) pregnant women who are unvaccinated and 2) pregnant women who have received an influenza or tetanus, diphtheria, and acellular pertussis (Tdap) vaccine during pregnancy.
Milestones for evaluation and reporting	• C4591015: Primary endpoints completion: 30 April 2023. • C4591009: • Protocol submission: 31 August 2021 • Monitoring report submission: 31 October 2022 • Interim Analysis submission: 31 October 2023 • Final study report submission: 31 October 2025. • C4591011: • Interim study reports[b] will be submitted on the following dates based on data collected post-EUA in target populations: o 31 December 2021 o 30 June 2022 o 31 December 2022

Table 43. Action Plan for Missing Information "Use in Pregnancy and Lactation"

	• Final study report submission: 31 December 2023. • C4591022: • Protocol submission: 01 July 2021 • Interim reports submission: o 31 January 2022 o 31 January 2023 o 31 January 2024 o 31 January 2025 • Final study report submission: 01 December 2025

a. Study assesses pregnancy only.
b. FDA was informed (Response to FDA 12 May 2021 - Information Request Regarding Active Surveillance Studies) that the first milestone (Interim Report submission due 30 June 2021) is delayed due to a change in study collaboration; therefore, it has been removed from in this table.

Table 44. Action Plan for Missing Information "Vaccine Effectiveness"

Action proposed	• 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. • BNT162-01 cohort 13: Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses.
Objective of proposed actions	• C4591014: To estimate the effectiveness of 2 doses of BNT162b2 against hospitalization and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection. • WI235284: To estimate the effectiveness of 2 doses of BNT162b2 against hospitalization for acute respiratory illness due to SARS-CoV-2 infection. • WI255886: To estimate the effectiveness of 2 doses of BNT162b2 against hospitalization for acute respiratory illness due to SARS-CoV-2 infection. • BNT-162-01 cohort 13: To assess potentially protective immune responses in immunocompromised adults.
Rationale for proposed actions	• C4591014: To determine the effectiveness of BNT162b2 when administered outside of the clinical setting. • WI235284: To determine the effectiveness of BNT162b2 when administered outside of the clinical setting. • WI255886: To determine the effectiveness of BNT162b2 when administered outside of the clinical setting. • BNT-162-01 cohort 13: To determine whether the BNT162b2 has potential to protect immunocompromised adults.

Table 44. Action Plan for Missing Information "Vaccine Effectiveness"

Monitoring by the sponsor for safety issue and proposed actions	• C4591014: Use of primary and secondary data sources to monitor COVID-19 infection in vaccinated individuals. • WI235284: Use of primary and secondary data sources to monitor COVID-19 infection in vaccinated individuals. • WI255886: Use of primary and secondary data sources to monitor COVID-19 infection in vaccinated individuals. • BNT-162-01 cohort 13: Reactogenicity, AE and SAE assessment.
Milestones for evaluation and reporting	• C4591014: Final CSR submission: 30 June 2023. • WI235284: Final CSR submission: 30 June 2023. • WI255886: Final CSR submission: 30 June 2023. • BNT-162-01 cohort 13: First IA submission: 30 September 2021.

Table 45. Action Plan for Missing Information "Use in Paediatric Individuals <12 Years of Age"

Actions proposed	• 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 RNA vaccine candidates against COVID-19 in healthy individuals[a]. Randomised placebo-controlled study in 2000 participants (1000 active recipients) of 2 doses of BNT162b2 at a 21-day interval. • 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 RNA vaccine candidate against COVID-19 in healthy children <12 years of age. Phase 1: open-label dose finding portion up to 3 age groups (participants ≥5 to <12 years, ≥2 to <5 years, and ≥6 months to <2 years of age) with 16 participants per dose level. Dose finding is being initiated in this study in participants ≥5 to <12 years of age based on the acceptable blinded safety assessment of the 30-µg dose in 12- to 15-year-olds in the C4591001 study. The purpose of Phase 1 is to identify preferred dose level(s) of BNT162b2 from up to 3 different dose levels in each age group. Phase 2/3: Children ≥5 to <12 years of age are randomized 2:1 at selected dose level of BNT162b2 at a 21-day interval (2250 total subjects; 1500 active vaccine). Children 2 to < 5 years and 6 to 23 months of age randomized 2:1 placebo controlled at selected dose level of BNT162b2 at a 21-day interval (1125 total subjects per age group; 750 active vaccine per age group). • C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States.

Table 45. Action Plan for Missing Information "Use in Paediatric Individuals <12 Years of Age"

Objective of proposed actions	• C4591001 ≥12 to ≤15 years of age: Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response compared to subjects 16-25 years of age. • C4591007 <12 years of age: Dose selection. Safety compared to placebo and immune-non-inferiority by 3 age cohorts of neutralizing antibody immune response compared to subjects 16-25 years of age. Efficacy if sufficient cases accrue. • C4591009: To assess the occurrence of safety events of interest in a general US population (<12 and ≥12 to ≤15 years of age) within selected data sources participating in the Sentinel System.
Rationale for proposed actions	• C4591001 ≥12 to ≤15 years of age: Need to collect evidence of safety and effectiveness to support immunization in this age group. • C4591007 <12 years of age: Need to collect evidence of safety and effectiveness to support immunization in this age group. • C4591009: Long-term surveillance of large numbers of individuals (<12 and ≥12 to ≤15 years of age) vaccinated with the BNT162b2 is necessary to confirm the safety profile demonstrated in the clinical study in a broader population under real-world conditions.

Monitoring by the sponsor for safety issue and proposed actions	• C4591001 ≥12 to ≤15 years of age:
	  • Electronic diary for reactogenicity 7 days following each dose of vaccine.
	  • Adverse events for one month after second dose.
	  • Serious Adverse Events for 6 months after the second dose.
	  • Related SAEs and related deaths for 24 months after the second dose.
	  • Collection of COVID-19 and MIS-C cases up to 24 months after the second dose.
	• C4591007 <12 years of age:
	  • Electronic diary for reactogenicity 7 days following each dose of vaccine.
	  • Adverse events for one month after second dose.
	  • Serious Adverse Events for 6 months after the second dose.
	  • Related SAEs and related deaths for 24 months after the second dose.
	  • Collection of COVID-19 and MIS-C cases up to 24 months after the second dose.
	• C4591009: < 12 and ≥12 to ≤15 years of age
	  • Longitudinal medical care information on outpatient medication dispensing, vaccine administrations, and inpatient and outpatient diagnoses and procedures in addition to adjudication of select events via medical records.
	  • Incidence rates and comparative incidence rate ratios of safety events of interest (AESIs from FDA's BEST System[70] and CDC's Vaccine Safety Datalink[71] in addition to vaccine-associated enhanced respirator disease).
	  • Study period to start on date that BNT162b2 became available under EUA (December 11, 2020) and will end a minimum of 3 years after this date.
	  • Risk windows will be defined for safety events of interest that have a hypothesized increased risk during specific time periods following vaccination. For other safety events of interest, patients will be followed for a maximum of 1 year.

Table 45. Action Plan for Missing Information "Use in Paediatric Individuals <12 Years of Age"

Milestones for evaluation and reporting	• C4591001 ≥12 to ≤15 years of age:
	  • First report with up to 1-month post dose 2 (safety): 30 April 2021
	  • Further reports:
	  – 6-month post dose 2 (safety): 31 October 2021[b]
	  – 24-month post dose 2 (safety): 30 April 2023[c].
	• C4591007 <12 years of age:
	  • First report with up to 1-month post dose 2 in ≥5 to <12 years of age (safety): 30 September 2021
	  • Further reports:
	  – 6-month post dose 2 (safety): 31 March 2022
	  – 24-month post dose 2 (safety): 30 September 2023.
	• C4591009:
	  • Protocol submission: 31 August 2021
	  • Monitoring report submission: 31 October 2022
	  • Interim Analysis submission: 31 October 2023
	  • Final study report submission: 31 October 2025.

a. Study originally included in the PVP to address the Missing Information "Use in pediatric individuals < 16 years of age".
b. Due date updated from 31 July 2021 because the last subject visit for this group will not be until September 2021.
c. Due updated from 31 January 2023 for the same reason above..

3.1.4. Summary of Actions to be Completed, Including Milestones

Table 46. Summary of Safety Concerns and Action Plans

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
Myocarditis and Pericarditis	C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States. *Planned*	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System	• Protocol submission: • Monitoring report submission: • Interim analysis submission: • Final study report submission:	• 31 August 2021 • 31 October 2022 • 31 October 2023 • 31 October 2025
	C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the US Department of Defense population following Emergency Use Authorization *Planned*	To assess whether individuals in the US DoD Military Health System (MHS) experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the Pfizer-BioNTech COVID-19 Vaccine.	• Interim reports submission:[a] • Final study report submission:	• 31 December 2021 30 June 2022 31 December 2022 • 31 December 2023
	C4591012: Post-emergency use authorization active safety surveillance study among individuals in the Veteran's Affairs Health System receiving Pfizer-BioNTech COVID-19 Vaccine. *Ongoing*	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the Pfizer-BioNTech COVID-19 Vaccine	• Interim reports submission: • Final study report submission:	• 30 June 2021 31 December 2021 30 June 2022 31 December 2022 • 31 December 2023
Anaphylaxis	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 RNA vaccine candidates against COVID-19 in healthy individuals.	To evaluate the safety, tolerability, immunogenicity, and efficacy of BNT162b2. An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence	• CSR submission upon regulatory request: • CSR submission 6-month post Dose 2: • Final CSR submission with supplemental follow-up:	• At any time • 31 May 2021 • 31 August 2023

Table 46. Summary of Safety Concerns and Action Plans

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
	Ongoing	of VAED/VAERD. Surveillance is planned for 2 years following Dose 2.		
	C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States. *Planned*	To assess the occurrence of safety events of interest in the general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System.	• Protocol submission: • Monitoring report submission: • Interim analysis submission: • Final study report submission:	• 31 August 2021 • 31 October 2022 • 31 October 2023 • 31 October 2025
	C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the US Department of Defense population following Emergency Use Authorization. *Planned*	To assess whether individuals in the US DoD Military Health System (MHS) experience increased risk of safety events of interest, following receipt of the BNT162b2.	• Interim reports submission[a]: • Final study report submission:	• 31 December 2021 30 June 2022 31 December 2022 • 31 December 2023
Anaphylaxis *(Cont'd)*	C4591012: Post-emergency use authorization active safety surveillance study among individuals in the Veteran's Affairs Health System receiving Pfizer-BioNTech COVID-19 Vaccine. Ongoing	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following receipt of the BNT162b2.	• Interim reports submission: • Final study report submission:	• 30 June 2021 31 December 2021 30 June 2022 31 December 2022 • 31 December 2023

Table 46. Summary of Safety Concerns and Action Plans

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	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 RNA vaccine candidates against COVID-19 in healthy individuals. *Ongoing*	To evaluate the safety, tolerability, immunogenicity, and efficacy of BNT162b2. An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may suggest the occurrence of VAED/VAERD. Surveillance is planned for 2 years following Dose 2	• CSR submission upon regulatory request: • CSR submission 6-month post Dose 2: • Final CSR submission with supplemental follow-up:	• Any time • 31 May 2021 • 31 August 2023
	C4591008/C4591012: Post-authorization epidemiological safety studies using active and passive surveillance strategies for safety events, including severe or atypical COVID-19, among individuals receiving Pfizer-BioNTech COVID-19 Vaccine C4591008: *Ongoing* C4591012: *Ongoing*	To characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease, among individuals vaccinated with the BNT162b2 since EUA	• Interim reports submission: • Final study report submission:	• 30 June 2021 31 December 2021 30 June 2022 31 December 2022 • 31 December 2023
	C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the US Department of Defense population following Emergency Use Authorization *Planned*	To characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease, among individuals vaccinated with the BNT162b2 since EUA	• Interim reports submission[a] • Final study report submission	• 31 December 2021 30 June 2022 31 December 2022 • 31 December 2023
Vaccine-associated enhanced disease (VAED)	C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States	To characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease,	• Protocol submission: • Monitoring report submission:	• 31 August 2021 • 31 October 2022 • 31 October 2023

Table 46. Summary of Safety Concerns and Action Plans

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
including vaccine-associated enhanced respiratory disease (VAERD) *(Cont'd)*	*Planned*	among individuals vaccinated with the BNT162b2	• Interim analysis submission: • Final study report submission:	• 31 October 2025
Use in pregnancy and lactation	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. *Ongoing*	To assess safety and immunogenicity of BNT162b2 in pregnant women. Exploratory objectives include: To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic BNT162b2 during pregnancy. To describe the safety of maternal immunization in infants born to breastfeeding maternal participants vaccinated with prophylactic BNT162b2 during pregnancy.	• Primary endpoints completion:	• 30 April 2023
Use in pregnancy and lactation *(Cont'd)*	C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense population following Emergency Use Authorization *Planned*	To assess whether sub-cohorts of interest, such as pregnant women, in the MHS experience increased risk of safety events of interest following receipt of the BNT162b2.	• Interim reports submission:[a] • Final study report submission:	• 31 December 2021 30 June 2022 31 December 2022 • 31 December 2023
	C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States. *Planned*	To assess whether pregnant women, experience increased risk of safety events of interest following receipt of the BNT162b2.	• Protocol submission: • Monitoring report submission: • Interim analysis submission: • Final study report submission:	• 31 August 2021 • 31 October 2022 • 31 October 2023 • 31 October 2025

Table 46. Summary of Safety Concerns and Action Plans

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
	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)/MotherToBaby Pregnancy Registry	To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age.	• Protocol submission: • Interim reports submission: Final study report submission:	• 01 July 2021 • 31 January 2022 31 January 2023 31 January 2024 31 January 2025 01 December 2025
Vaccine effectiveness	C4591014: Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California. *Planned*	To estimate the effectiveness of 2 doses of BNT162b2 against hospitalization and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.	• Final CSR submission:	• 30 June 2023
Vaccine effectiveness *(Cont'd)*	WI235284: Determining RSV Burden and Outcomes in Pregnant Women and Older Adults Requiring Hospitalization. Amendment for COVID VE/ Sub-study 6. *Planned*	To estimate the effectiveness of 2 dosed of BNT162b2 against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.	• Final CSR submission:	• 30 June 2023

Table 46. Summary of Safety Concerns and Action Plans

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
	WI255886: Avon Community Acquired Pneumonia Surveillance Study: A Pan-pandemic Acute Lower Respiratory Tract Disease Surveillance. *Planned*	To estimate the effectiveness of 2 doses of BNT162b2 against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.	• Final CSR submission:	• 30 June 2023
	BNT162-01 cohort 13: Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses. *Ongoing*	To assess potentially protective immune responses in immunocompromised adults.	• First IA submission:	• 30 September 2021

Table 46. Summary of Safety Concerns and Action Plans

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
Use in pediatric individuals <12 years of age	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 RNA vaccine candidates against COVID-19 in healthy individuals[b]. *Ongoing*	Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response compared to subjects 16-25 years of age.	• First report with up to 1-month post dose 2 (safety): • Report 6-month post dose 2 (safety): • Report 24-month post dose 2 (safety):	• 30 April 2021 • 31 October 2021[c] • 30 April 2023[d]
	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 RNA vaccine candidate against COVID-19 in healthy children <12 years of age. *Ongoing (started in March)*	Dose selection. Safety compared to placebo and immune-non-inferiority by 3 age cohorts of neutralizing antibody immune response compared to subjects 16-25 years of age. Efficacy if sufficient cases accrue.	• First report with up to 1-month post dose 2 (safety) in ≥5 to <12 years of age: • Report 6-month post dose 2 (safety) in ≥5 to <12 years of age: • Report 24-month post dose 2 (safety) in ≥5 to <12 years of age:	• 30 September 2021 • 31 March 2022 • 30 September 2023
	C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States. *Planned*	To assess the occurrence of safety events of interest in a general US population (< 12 and ≥ 12 to ≤15 years of age) within selected data sources participating in the Sentinel System.	• Protocol submission: • Monitoring report submission: • Interim analysis submission: • Final study report submission:	• 31 August 2021 • 31 October 2022 • 31 October 2023 • 31 October 2025

a. FDA was informed (Response to FDA – 12 May 2021 – Information Request Regarding Active Surveillance Studies) that the first milestone (Interim Report submission due 30 June 2021) is delayed due to a change in study collaboration; therefore, it has been removed from this table.
b. Study originally included in the PVP to address the Missing Information "Use in pediatric individuals < 16 years of age.
c. Due date updated from 31 July 2021 because the last subject visit for this group will not be until September 2021.
d. Due updated from 31 January 2023 for the same reason above.

ANNEX

3.2. Pharmacovigilance Methods

- BNT162b2 Vaccine: BNT162b2 Data Capture Aids:
    - Pfizer-BioNTech COVID-19 Vaccine VAED Data Capture Aid.
    - Pfizer-BioNTech COVID-19 Vaccine Anaphylactic Reaction Data Capture Aid.

3.2.1. List of Studies Included in the Pharmacovigilance Plan

C4591001

C4591007

C4591008

C4591009

C4591011

C4591012

C4591014

C4591015

C4591022

BNT162-01 cohort 13

WI235284

WI255886

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