

**PHARMACOVIGILANCE PLAN FOR**

**EMERGENCY USE AUTHORIZATION # 27034**

**OF**

**PFIZER-BIONTECH COVID-19 VACCINE**

**Date of Report: ~~20 JANUARY~~08 APRIL 2021**

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## LIST OF ABBREVIATIONS

Abbreviation	Definition of Term
<del>AE</del>	<del>adverse event</del>
A:G	albumin:globulin
AE	adverse event
AESI	adverse event of special interest
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 defence
ECDC	European Center for Disease Control
<del>ED</del>	<del>emergency department</del>
EEA	European Economic Area
eGFR	epidermal growth factor receptor
EU	European Union
EUA	emergency use authorization
<del>EU</del>	<del>European Union</del>
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

Abbreviation	Definition of Term
LNP	lipid nanoparticle
MAH	marketing authorization holder
<del>mRNA</del> MedDRA	<del>messenger ribonucleic acid</del> <a href="#">Medical Dictionary for Regulatory Activities</a>
MERS-CoV	<a href="#">middle east respiratory syndrome–coronavirus</a>
MHS	<a href="#">military health system</a>
MIS-C	<a href="#">multisystem inflammatory syndrome in children</a>
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	<a href="#">messenger ribonucleic acid</a>
NDA	new drug application
NHP	nonhuman primate
NICE	<a href="#">National Institute for Health and Care Excellence</a>
OCS	<a href="#">oral corticosteroids</a>
PK	pharmacokinetic
PVP	pharmacovigilance plan
RBC	red blood cell
RNA	ribonucleic acid
RR	<a href="#">relative risk</a>
SAE	<a href="#">serious adverse event</a>
SARS	severe acute respiratory syndrome
<a href="#">SARS-CoV-1</a>	<a href="#">severe acute respiratory syndrome coronavirus 1</a>
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
siRNA	small-interfering RNA
SMQ	<a href="#">standardised MedDRA query</a>
TESSy	The European Surveillance System
Th	<a href="#">T helper lymphocyte</a>
UK	United Kingdom
US	United States
USP	<a href="#">United States pharmacopeia</a>
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	<a href="#">women of child bearing potential</a>

## 1. INTRODUCTION

### 1.1. Product Details

**Table 1. Product Details<sup>a</sup>**

<b>Product</b>	Pfizer-BioNTech COVID-19 vaccine is a nucleoside-modRNA encoding the viral spike glycoprotein S of SARS-CoV-2.
<b>Brief description of the product</b>	<p><u>Chemical class:</u> Nucleoside-modRNA <del>encapsulated</del> <u>formulated</u> in <del>LNP</del> <u>lipid particles</u>.</p> <p><u>Mechanism of Action:</u> The <del>LNP</del> <u>enables entry</u> modRNA in the Pfizer BioNTech COVID-19 Vaccine is <u>formulated in lipid particles, which enable delivery of the RNA</u> into host cells <del>and to allow</del> expression of the <u>SARS-CoV-2 S protein-antigen</u>. The vaccine elicits <del>both antibody and cellular</del> <u>immune responses to the viral spike glycoprotein S, which are known to contribute to the mechanism of protection</u> the S antigen, which protects against COVID-19.</p> <p><u>Important information about its composition:</u> The Pfizer-BioNTech COVID-19 vaccine:</p> <ul style="list-style-type: none"> <li>is <u>supplied as a white to off-white, sterile, preservative-free, frozen suspension; in multiple dose vials;</u></li> <li><u>each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine.</u></li> <li><u>Each dose of the Pfizer BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S-protein) glycoprotein of SARS-CoV-2;</u></li> <li><u>Each dose of the Pfizer BioNTech COVID-19 vaccine also includes the following inactive 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.</u></li> </ul>
<b>Indication</b>	<p><u>Proposed:</u> <del>Prevention of</del> <u>Active immunization to prevent</u> COVID-19 <u>caused by SARS-CoV-2</u> in individuals <del>16-12</del> years of age and older.</p>
<b>Dosage and route of administration</b>	<p><u>Proposed:</u> Series of two doses (0.3 mL each) <del>21 days</del> <u>3 weeks</u> apart, <del>IM administered;</del> <u>for intramuscular injection only.</u></p>

a. Pfizer-BioNTech COVID-19 vaccine Full EUA Prescribing Information (~~Module 1.14~~)

Data Lock Point / <u>Data cut-off:</u>	12-15 years of age	<del>14 November 2020</del> <u>13 March 2021</u> (Pfizer Clinical Database)
		<u>28 February 2021</u> (Pfizer Safety Database)
	<u>16 years and older</u>	<u>14 November 2020</u> (Pfizer Clinical Database)
		02 October 2020 (BioNTech Clinical Database)
		<u>31 December 2020</u> (Pfizer Safety Database for Anaphylaxis safety concern)



## 2. SAFETY SPECIFICATION

### 2.1. Elements of the Safety Specification

#### 2.1.1. Non-Clinical

Nonclinical evaluation of BNT162b2Pfizer-BioNTech COVID-19 vaccine 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. A DART study is ongoing in rats. No additional toxicity studies are planned for BNT162b2Pfizer-BioNTech COVID-19 vaccine.

Nonclinical studies in mice and NHP for BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) demonstrated both a strong neutralizing antibody response and a Th1 -type CD4<sup>+</sup> and an IFN $\gamma$ <sup>+</sup> CD8<sup>+</sup> T-cell response. The Th1 profile is characterized by a strong IFN $\gamma$ , 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.<sup>1</sup> Rhesus macaques (Study VR-VRT-10671) that had received two IM immunizations with 100  $\mu$ g BNT162b2Pfizer-BioNTech COVID-19 vaccine or saline 21 days apart were challenged with  $1.05 \times 10^6$  plaque forming units of SARS-CoV-2 (strain USA-WA1/2020), split equally between the intranasal and intratracheal routes.<sup>2</sup> BNT162b2Pfizer-BioNTech COVID-19 vaccine 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 as Pfizer-BioNTech COVID-19 vaccine, 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 like Pfizer-BioNTech COVID-19 vaccine, 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 was not detected 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 Pfizer--BioNTech COVID-19 vaccine 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. Pfizer-BioNTech COVID-19 vaccine (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. ~~AA GLP-compliant~~ DART study in Wistar Han rats ~~is ongoing~~ has also been completed. Safety pharmacology, genotoxicity and carcinogenicity studies have not been conducted, in accordance with the 2005 WHO vaccine guideline.<sup>3</sup>

The IM route of exposure was selected for nonclinical ~~investigation~~ 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 Pfizer--BioNTech COVID-19 vaccine 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 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 ~~observed~~ reported in rats treated with the licensed LNP-siRNA pharmaceutical Onpattro™ (NDA # 210922) but have not been observed in humans treated with this biotherapeutic<sup>4</sup> 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 Pfizer--BioNTech COVID-19 vaccine (V8) without evidence of cholestasis or hepatobiliary injury but was not recapitulated in the second repeat dose-toxicity study with Pfizer--BioNTech COVID-19 vaccine (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 Pfizer--BioNTech COVID-19 vaccine, 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 Pfizer--BioNTech COVID-19 vaccine. 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 only test article-related liver microscopic finding, was not associated with any microscopic evidence of hepatic injury or hepatic functional effects (~~ie, i.e.,~~ liver functional enzymes were not elevated) and ~~is believed to may~~ be associated with hepatocyte uptake of the LNP lipids.<sup>5</sup> 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 Pfizer–BioNTech COVID-19 vaccine. A robust immune response was elicited to the Pfizer–BioNTech COVID-19 vaccine antigen.

Administration of Pfizer-BioNTech COVID-19 vaccine to female rats twice before the start of mating and twice during gestation at the human clinical dose 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 Pfizer-BioNTech COVID-19 vaccine 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 Pfizer–BioNTech COVID-19 vaccine 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 Pfizer–BioNTech COVID-19 vaccine from nonclinical studies and their relevance to human usage are presented in ~~Table 2~~ 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 <sup>a,b</sup>	Relevance to Human Usage
<b>Pharmacology</b>	
<b>NHP Challenge Model</b> <ul style="list-style-type: none"> <li>No evidence of vaccine-elicited disease enhancement.</li> </ul>	<ul style="list-style-type: none"> <li>Suggests low risk of vaccine-enhanced disease in humans; being investigated in CTs.</li> </ul>
<b>Toxicity</b>	
<b>Injection site reactions:</b> <ul style="list-style-type: none"> <li>Injection site reactions were common and reversible or showed signs of reversibility at the end of the 3-week recovery period in nonclinical studies.</li> </ul> <b>Inflammation and immune activation:</b> <ul style="list-style-type: none"> <li>Evidence of inflammation or immune activation was common, reversible, and included transiently higher body temperature, higher circulating WBCs, and higher acute phase reactants. Secondly, transiently lower body weights, reticulocytes, platelets, and RBC mass parameters were observed.</li> </ul>	<ul style="list-style-type: none"> <li>In common with other vaccines, Pfizer-BioNTech COVID-19 vaccine administration has the potential to generate injection site reactions such as edema and erythema at the injection sites.</li> <li>In common with all vaccines, Pfizer-BioNTech COVID-19 vaccine administration has the potential to generate inflammation which can lead to increased body temperature, higher circulating WBCs and higher acute phase proteins.</li> <li>Decreased reticulocytes have not been observed in humans treated with the LNP-siRNA pharmaceutical Onpatro<sup>4</sup>, suggesting this finding in rats is a species-specific effect.</li> <li>Pfizer-BioNTech COVID-19 vaccine 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.</li> </ul>
<b>Developmental and Reproductive Toxicity</b> <ul style="list-style-type: none"> <li><u>No vaccine-related effects on female fertility or the development of fetuses or offspring were observed in a DART study of Pfizer-BioNTech COVID-19 vaccine in rats.</u></li> </ul>	<ul style="list-style-type: none"> <li><u>No effects are anticipated in WOCBP, pregnant women or their offspring.</u></li> </ul>

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.<sup>3</sup> In addition, the components of the vaccine construct are lipids and RNA and are not expected to have carcinogenic or genotoxic potential.

~~b. A DART study evaluating Pfizer BioNTech COVID-19 vaccine will be completed in Q1 2021.~~

## 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 44,000~~46,333~~ participants, which would slightly enhance the ability to detect AEs. However, rarer events might not be detected.

Participants ~~are in the pivotal study were initially~~ planned to be followed for up to 24 months. ~~This is particularly relevant for assessing 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

~~Pfizer BioNTech COVID-19 vaccine has been developed for the prevention of COVID-19 caused by the virus SARS-CoV-2 for use in participants ≥16 years of age.~~

BioNTech is conducting a ~~German~~ 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 vaccine candidates individually to inform the overall clinical development of a Pfizer-BioNTech COVID-19 vaccine.

BNT162-01 is not conducted under the US IND application but is being conducted under a German Clinical Trial Application. ~~The protocol for this study is provided in Module 5 (Module 5.3.5.1 Clinical Study Protocol BNT162-01) of IND 019736. Please refer to Module 1.4.4 for location details.~~

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—~~Please refer to Module 1.4.4 for Study C4591001 location details).~~).

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. BNT162b2Pfizer-BioNTech COVID-19 vaccine 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 BNT162b2Pfizer-BioNTech COVID-19 vaccine was more favorable than BNT162b1 in both younger and older adults with similar immunogenicity results;
- in the NHP challenge study (VR-VTR-10671—~~Cross ref. with, see Section 2.1.1~~Section 2.1.1), a trend toward earlier clearance of BNT162b2Pfizer-BioNTech COVID-19 vaccine 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 adolescents participants 16 to 17 years of age to be evaluated with the 18- to 55-year-old cohort, as well as enrollment of a 12- to ≤1615-year-old cohort, and immunogenicity data from adolescents participants 12- to ≤16 years of age 15-year-old cohort (~~Table 5—adolescents 12 to ≤16 years~~) Table 14 through Table 18) are anticipated to bridge to the 16- to 25-year-old cohort.

The initial efficacy ~~evaluation is 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 cases reported by 13 March 2021.

Ongoing Pfizer-BioNTech COVID-19 vaccine 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

~~Clinical study exposure data are being provided for ongoing studies as of 14 November 2020 for study C4591001 and as of 02 October 2020 for study BNT162-01.~~

~~At the DLP, a total of 43,734 participants were vaccinated in the Pfizer-BioNTech COVID-19 vaccine clinical development program:~~

- ~~• 21,937 participants were exposed to BNT162b2 (Pfizer-BioNTech COVID-19 vaccine), including 96 participants from study BNT162-01.~~
- ~~• 21,797 participants were exposed to PLACEBO (none from study BNT162-01).~~

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 14 November 2020, a total of 43,734 participants were vaccinated in the Pfizer-BioNTech COVID-19 vaccine clinical development program:

- 21,937 participants were exposed to Pfizer-BioNTech COVID-19 vaccine, including 96 participants from study BNT162-01.
- 21,797 participants were exposed to Placebo (none from study BNT162-01).

Exposure to Pfizer-BioNTech COVID-19 vaccine for participants imaged 16 years and older in the 2 ongoing studies by number of doses, and demographic characteristics is shown in ~~Table 8~~ Table 3 through Table 13.

In addition, exposure in clinical studies in special populations is provided in Table 19.

### Participants 12 to 15 years of age

Clinical study exposure data for the 12- to ≤15 years of age is 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 Pfizer-BioNTech COVID-19 vaccine in the Blinded-Placebo Controlled Follow-up period;



- 49 participants who originally received placebo, then received 1 dose of Pfizer-BioNTech COVID-19 vaccine in the Open-Label Follow-up period after unblinding.

Exposure to Pfizer-BioNTech COVID-19 vaccine for participants aged 12- to  $\leq 15$  years of age by number of doses and demographic characteristics is shown in Table 14 through Table 18. Note: Data for 12- to  $\leq 15$  years of age at the cut-off date of 14 November 2020 are shown in Table 5, while data for 12- to  $\leq 15$  years of age at the cut-off date of 13 March 2021 are displayed in Table 14 through Table 18.

In addition, exposure in clinical studies in special populations is provided in Table 20 and Table 21.

**Table 3. Exposure to BNT162b2 by Age Group and Dose (C4591001)**

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	61	61
2 Doses	77	154
Total	138	215
≥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	825	825
2 Doses	11830	23660
Total	12655	24485
>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	323	323
2 Doses	8629	17258
Total	8952	17581

Note: 30 µg includes data from phase 1 and phase 2/3.

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**Table 4. 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
<b>≥18 years to ≤55 years</b>		
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	11	22
Total	12	23
Vaccine 20 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24
Vaccine 30 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24

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**Table 4. 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
<b>&gt;55 years</b>		
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	12	24
Total	12	24
Vaccine 20 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24
Vaccine 30 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24

PFIZER CONFIDENTIAL SDTM Creation: 03NOV2020 (21:23) Source Data: adsl Table Generation: 18NOV2020  
(14:42) (Cutoff date: 02OCT2020, Snapshot Date: 02OCT2020)  
Output File: ex\_b2\_age\_dose2.rtf

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**Table 5. Exposure to BNT162b2 by Age Group and Dose – Children and Elderly Subjects (C4591001)**

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	1	1
2 Doses	48	96
Total	49	97
≥65 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	121	121
2 Doses	4435	8870
Total	4556	8991
Note: 30 µg includes data from phase 1 and phase 2/3. PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 19NOV2020 (00:22) (Cutoff date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: (CDISC)/C4591001 RMP Phase1 2 3/adsl s913		

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**Table 6. Exposure to BNT162b2 by Dose (Totals) (C4591001)**

<b>Dose Exposure (Number of Doses Received)</b>	<b>Number of Subjects Exposed to BNT162b2</b>	<b>Total Number of Vaccine Doses</b>
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	1209	1209
2 Doses	20536	41072
Total	21745	42281

Note: 30 µg includes data from phase 1 and phase 2/3.  
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation:  
19NOV2020 (00:22) (Cutoff date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:  
(CDISC)/C4591001\_RMP\_Phase1\_2\_3/adsl\_s922

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**Table 7. Exposure to BNT162b2 by Dose (Totals) (BNT162-01)**

<b>Dose Exposure (Number of Doses Received)</b>	<b>No. of Subjects Exposed to BNT162b2</b>	<b>Total No. of Vaccine Doses</b>
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: 03NOV2020 (21:23) Source Data: adsl Table Generation: 17NOV2020 (13:08) (Cutoff date: 02OCT2020, Snapshot Date: 02OCT2020)  
Output File: ex\_b2\_dose.rtf

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**Table 8. Exposure to BNT162b2 by Dose, Age Group, and Gender (C4591001)**

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
>55 years	2	10	4	20
Total	7	17	14	34
Vaccine 20 µg				
≥18 years to ≤55 years	6	6	12	12
>55 years	5	7	10	14
Total	11	13	22	26
Vaccine 30 µg				
≥16 years to ≤17 years	75	63	117	98
≥18 years to ≤55 years	6437	6218	12397	12088
>55 years	4680	4272	9177	8404
Total	11192	10553	21691	20590

Note: 30 µg includes data from phase 1 and phase 2/3.

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**Table 9. Exposure to BNT162b2 by Dose, Age Group, and Gender (BNT162-01)**

Dose Age Group	No. of Subjects Exposed to BNT162b2		Total No. of Vaccine Doses	
	Male	Female	Male	Female
Vaccine 1 µg				
≥18 years to ≤55 years	7	5	14	9
>55 years	0	0	0	0
Total	7	5	14	9
Vaccine 3 µg				
≥18 years to ≤55 years	5	7	10	14
>55 years	0	0	0	0
Total	5	7	10	14
Vaccine 10 µg				
≥18 years to ≤55 years	4	8	8	15
>55 years	8	4	16	8
Total	12	12	24	23
Vaccine 20 µg				
≥18 years to ≤55 years	2	10	4	20
>55 years	6	6	12	12
Total	8	16	16	32
Vaccine 30 µg				
≥18 years to ≤55 years	8	4	16	8
>55 years	4	8	8	16
Total	12	12	24	24

PFIZER CONFIDENTIAL SDTM Creation: 03NOV2020 (21:23) Source Data: adsl Table Generation: 18NOV2020  
(15:12) (Cutoff date: 02OCT2020, Snapshot Date: 02OCT2020)  
Output File: ex\_b2\_age\_dose\_sex2.rtf

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**Table 10. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001)**

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
<b>Subjects ≥16 years to ≤17 years</b>		
Vaccine 30 µg		
Racial Origin		
White	102	158
Black or African American	21	35
Asian	7	8
Native Hawaiian or other Pacific Islander	2	4
Multiracial	6	10
Total	138	215
Ethnic Origin		
Hispanic/Latino	17	24
Non-Hispanic/non-Latino	121	191
Total	138	215
<b>Subjects ≥18 years to ≤55 years</b>		
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
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

**Table 10. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001)**

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg		
Racial Origin		
White	9917	19153
Black or African American	1400	2725
Asian	681	1332
American Indian or Alaska Native	118	211
Native Hawaiian or other Pacific Islander	40	79
Multiracial	418	825
Not reported	81	160
Total	12655	24485
Ethnic Origin		
Hispanic/Latino	4001	7807
Non-Hispanic/non-Latino	8590	16557
Not reported	64	121
Total	12655	24485
Subjects >55 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	12	24
Total	12	24
Ethnic Origin		
Non-Hispanic/non-Latino	12	24
Total	12	24

**Table 10. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001)**

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg		
Racial Origin		
White	7842	15403
Black or African American	671	1312
Asian	248	490
American Indian or Alaska Native	42	80
Native Hawaiian or other Pacific Islander	15	29
Multiracial	112	223
Not reported	22	44
Total	8952	17581
Ethnic Origin		
Hispanic/Latino	1655	3254
Non-Hispanic/non-Latino	7241	14215
Not reported	56	112
Total	8952	17581
Note: 30 µg includes data from phase 1 and phase 2/3. PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 19NOV2020 (00:22) (Cutoff date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: (CDISC)/C4591001_RMP_Phase1_2_3/adsl_s942		

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**Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)**

Age Group	No. of Subjects Exposed to	
Dose	BNT162b2	Total No. of Vaccine Doses
Race/Ethnic Origin		
<b>Subjects ≥18 to ≤55 years</b>		
Vaccine 1 µg		
Racial Origin		
White	12	23
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	23
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	23
Not reported	0	0
Unknown	0	0
Total	12	23

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**Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)**

Age Group	No. of Subjects Exposed to	
Dose	BNT162b2	
Race/Ethnic Origin	Total No. of Vaccine Doses	
Subjects ≥18 to ≤55 years		
Vaccine 3 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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**Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)**

Age Group	No. of Subjects Exposed to	
Dose	BNT162b2	
Race/Ethnic Origin	Total No. of Vaccine Doses	
<b>Subjects</b> ≥18 to ≤55 years		
Vaccine 10 µg		
Racial Origin		
White	12	23
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	23
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	23
Not reported	0	0
Unknown	0	0
Total	12	23

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**Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)**

Age Group	No. of Subjects Exposed to	
Dose	BNT162b2	
Race/Ethnic Origin	Total No. of Vaccine Doses	
<b>Subjects ≥18 to ≤55 years</b>		
Vaccine 20 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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**Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)**

Age Group	No. of Subjects Exposed to	
Dose	BNT162b2	Total No. of Vaccine Doses
Race/Ethnic Origin		
<b>Subjects ≥18 to ≤55 years</b>		
Vaccine 30 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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**Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)**

Age Group	No. of Subjects Exposed to	
Dose	BNT162b2	Total No. of Vaccine Doses
Race/Ethnic Origin		
<b>Subjects</b> >55 to ≤85 years		
Vaccine 1 µg		
Racial Origin		
White	0	0
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	0	0
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	0	0
Not reported	0	0
Unknown	0	0
Total	0	0

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**Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)**

Age Group	No. of Subjects Exposed to	
Dose	BNT162b2	Total No. of Vaccine Doses
Race/Ethnic Origin		
<b>Subjects</b> >55 to ≤85 years		
Vaccine 3 µg		
Racial Origin		
White	0	0
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	0	0
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	0	0
Not reported	0	0
Unknown	0	0
Total	0	0

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**Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)**

Age Group	No. of Subjects Exposed to	
Dose	BNT162b2	
Race/Ethnic Origin	Total No. of Vaccine Doses	
<b>Subjects</b> >55 to ≤85 years		
Vaccine 10 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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**Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)**

Age Group	No. of Subjects Exposed to	
Dose	BNT162b2	
Race/Ethnic Origin	Total No. of Vaccine Doses	
<b>Subjects</b> >55 to ≤85 years		
Vaccine 20 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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**Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)**

Age Group	No. of Subjects Exposed to	
Dose	BNT162b2	Total No. of Vaccine Doses
Race/Ethnic Origin		
<b>Subjects &gt;55 to ≤85 years</b>		
Vaccine 30 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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Output File: ex\_b2\_age\_dose\_race.rtf

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**Table 12. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001)**

<b>Dose Race/Ethnic Origin</b>	<b>Number of Subjects Exposed to BNT162b2</b>	<b>Total Number of Vaccine Doses</b>
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		
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	17861	34714
Black or African American	2092	4072
Asian	936	1830
American Indian or Alaska Native	160	291
Native Hawaiian or other Pacific Islander	57	112
Multiracial	536	1058
Not reported	103	204
Total	21745	42281
Ethnic Origin		
Hispanic/Latino	5673	11085
Non-Hispanic/non-Latino	15952	30963
Not reported	120	233
Total	21745	42281

Note: 30 µg includes data from phase 1 and phase 2/3.

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 19NOV2020 (00:23) (Cutoff date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: (CDISC)/C4591001\_RMP\_Phase1\_2\_3/adsl\_s952

**Table 13. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)**

<b>Dose Race/Ethnic Origin</b>	<b>No. of Subjects Exposed to BNT162b2</b>	<b>Total No. of Vaccine Doses</b>
Vaccine 1 µg		
Racial Origin		
White	12	23
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	23
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	23
Not reported	0	0
Unknown	0	0
Total	12	23

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**Table 13. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)**

<b>Dose Race/Ethnic Origin</b>	<b>No. of Subjects Exposed to BNT162b2</b>	<b>Total No. of Vaccine Doses</b>
Vaccine 3 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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**Table 13. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)**

<b>Dose Race/Ethnic Origin</b>	<b>No. of Subjects Exposed to BNT162b2</b>	<b>Total No. of Vaccine Doses</b>
Vaccine 10 µg		
Racial Origin		
White	24	47
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	24	47
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	24	47
Not reported	0	0
Unknown	0	0
Total	24	47

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**Table 13. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)**

<b>Dose Race/Ethnic Origin</b>	<b>No. of Subjects Exposed to BNT162b2</b>	<b>Total No. of Vaccine Doses</b>
Vaccine 20 µg		
Racial Origin		
White	24	48
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	24	48
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	24	48
Not reported	0	0
Unknown	0	0
Total	24	48

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**Table 13. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)**

<b>Dose Race/Ethnic Origin</b>	<b>No. of Subjects Exposed to BNT162b2</b>	<b>Total No. of Vaccine Doses</b>
Vaccine 30 µg		
Racial Origin		
White	24	48
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	24	48
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	24	48
Not reported	0	0
Unknown	0	0
Total	24	48

PFIZER CONFIDENTIAL SDTM Creation: 03NOV2020 (21:23) Source Data: adsl Table Generation: 17NOV2020  
(13:09) (Cutoff date: 02OCT2020, Snapshot Date: 02OCT2020)  
Output File: ex\_b2\_dose\_race.rtf

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**Table 14. Exposure to BNT162b2 (~~30 µg~~) by ~~Special Population (C4591001)~~ – All Subjects 12-15 Years – Blinded Placebo-Controlled Follow-up Period**

<u>Population Age Group</u> <u>Dose</u> <u>Exposure (Number of Doses Received)</u>	<u>Number of Subjects</u> <u>Exposed to BNT162b2 (<del>30 µg</del>)</u> <u>(N<sup>a</sup>=<del>21720</del>)</u> <u>n<sup>b</sup></u>	<u>Total Number of</u> <u>Vaccine Doses</u>
<u>&gt;12 years to ≤15 years</u>	.	.
<u>Vaccine 30 µg</u>	.	.
<u>1 Dose</u>	<u>7</u>	<u>7</u>
<u>2 Doses</u>	<u>1124</u>	<u>2248</u>
<u>Total</u>	<u>1131</u>	<u>2255</u>

Note: 30 µg includes data from phase 1 and phase 2/3.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 01 APR2021 (14:39)

(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2\_unblinded/C4591001\_PVP\_BLA/adsl\_s914

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**Table 15. Exposure to BNT162b2 (C4591001) – All Subjects 12-15 Years – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

<u>Age Group</u> <u>Dose</u> <u>Exposure (Number of Doses Received)</u>	<u>Number of Subjects</u> <u>Exposed to BNT162b2</u>	<u>Total Number of</u> <u>Vaccine Doses</u>
>12 years to <15 years <sup>a</sup>	-	-
Vaccine 30 µg	-	-
1 Dose	30	30
2 Doses	19	38
Total	49	68

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.

Note: 30 µg includes data from phase 1 and phase 2/3.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 01 APR2021 (17:33)

(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2\_unblinded/C4591001\_PVP\_BLA/adsl\_s915

**Table 16. Exposure to BNT162b2 by Gender (C4591001) – All Subjects 12-15 Years – Blinded Placebo-Controlled Follow-up Period**

<u>Dose</u> <u>Age Group</u>	<u>Number of Subjects Exposed to</u> <u>BNT162b2</u>		<u>Total Number of Vaccine</u> <u>Doses</u>	
	<u>Male</u>	<u>Female</u>	<u>Male</u>	<u>Female</u>
Vaccine 30 µg	-	-	-	-
>12 years to <15 years	567	564	1128	1127

Note: 30 µg includes data from phase 1 and phase 2/3.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 01 APR2021 (18:25)

(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2\_unblinded/C4591001\_PVP\_BLA/adsl\_s9324

**Table 17. Exposure to BNT162b2 by Race/Ethnic Origin (C4591001) – All Subjects  
12-15 Years –  
Blinded Placebo-Controlled Follow-up Period**

<u>Age Group</u> <u>Dose</u> <u>Race/Ethnic Origin</u>	<u>Number of Subjects</u> <u>Exposed to BNT162b2</u>	<u>Total Number of</u> <u>Vaccine Doses</u>
-	-	-
>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

Note: 30 µg includes data from phase 1 and phase 2/3.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 01APR2021 (18:55)

(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2\_unblinded/C4591001\_PVP\_BLA/adsl\_s944

**Table 18. Exposure to BNT162b2 by Race/Ethnic Origin (C4591001) – All Subjects  
12-15 Years – Open-Label Follow-up Period – Subjects Who Originally  
Received Placebo and Then Received BNT162b2 After Unblinding**

<u>Age Group</u> <u>Dose</u> <u>Race/Ethnic Origin</u>	<u>Number of Subjects</u> <u>Exposed to BNT162b2</u>	<u>Total Number of</u> <u>Vaccine Doses</u>
-	-	-
>12 years to <15 years <sup>a</sup>	-	-
Vaccine 30 µg	-	-
Racial origin	-	-
White	45	62
Asian	3	5
Multiracial	1	1
Total	49	68
Ethnic origin	-	-
Hispanic/Latino	2	4

**Table 18. Exposure to BNT162b2 by Race/Ethnic Origin (C4591001) – All Subjects 12-15 Years – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

<u>Age Group</u> <u>Dose</u> <u>Race/Ethnic Origin</u>	<u>Number of Subjects</u> <u>Exposed to BNT162b2</u>	<u>Total Number of</u> <u>Vaccine Doses</u>
-		
Non-Hispanic/non-Latino	47	64
Total	49	68

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.  
Note: 30 µg includes data from phase 1 and phase 2/3.  
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 01 APR2021 (19:02)  
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:  
./nda2\_unblinded/C4591001\_PVP\_BLA/adsl\_s944\_open

**Table 19. Exposure to BNT162b2 (30 µg) by Special Population (C4591001)**

<u>Population</u>	<u>Number of Subjects</u> <u>Exposed</u> <u>to BNT162b2 (30 µg)</u> <u>(N<sup>a</sup>= 21720)</u> <u>n<sup>b</sup></u>	<u>Total Number</u> <u>of</u> <u>Vaccine Doses</u>
Subjects with any baseline comorbidity	10017	25215
AIDS/HIV	99	177
Any Malignancy + Metastatic Solid Tumor + Leukemia + Lymphoma	845	1660
Chronic Pulmonary Disease	1730	3379
Renal Disease	139	274
Rheumatic Disease	75	142
Mild Liver Disease + Moderate or Severe Liver Disease	145	282
Cerebrovascular Disease + Peripheral Vascular Disease + Myocardial Infarction + Congestive Heart Failure	645	1265
Dementia	7	14
Diabetes With/Without Chronic Complication	1693	3301
Hemiplegia or Paraplegia	4	8
Peptic Ulcer Disease	62	120
Obese (≥30.0 kg/m <sup>2</sup> )	7488	14593

a. N = number of subjects in the specified group.

b. n = Number of subjects reporting at least 1 occurrence of any comorbidity or BMI (≥30.0 kg/m<sup>2</sup>).



**Table 19. Exposure to BNT162b2 (30 µg) by Special Population (C4591001)**

<u>Population</u>	<u>Number of Subjects Exposed to BNT162b2 (30 µg)</u> ( <u>N<sup>a</sup> = 21720</u> ) <u>n<sup>b</sup></u>	<u>Total Number of Vaccine Doses</u>
-------------------	---	--------------------------------------

Note: Comorbidity is based 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 reporting at least 1 occurrence of any comorbidity or BMI ( $\geq 30.0 \text{ kg/m}^2$ )~~

~~b. N = number of subjects in the specified group~~

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:04) Source Data: admh Table Generation: 18NOV2020 (23:16) (Cutoff date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: (CDISC)/C4591001 RMP Phase1 2 3/admh s953

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**Table 20. Exposure to BNT162b2 (30 µg) by Special Population (C4591001) – All Subjects 12-15 years – Blinded Placebo-Controlled Follow-up Period**

<b>Population</b>	<b>Number of Subjects Exposed to BNT162b2 (30 µg) (N<sup>a</sup>=1131) n<sup>b</sup></b>	<b>Total Number of Vaccine Doses</b>
<u>Subjects with any baseline comorbidity</u>	<u>248</u>	<u>525</u>
<u>Chronic Pulmonary Disease</u>	<u>118</u>	<u>233</u>
<u>Mild Liver Disease + Moderate or Severe Liver Disease</u>	<u>2</u>	<u>4</u>
<u>Diabetes With/Without Chronic Complication</u>	<u>2</u>	<u>4</u>
<u>Obese</u>	<u>143</u>	<u>284</u>

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 ≥95<sup>th</sup> 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\_12

**Table 21. Exposure to BNT162b2 (30 µg) by Special Population (C4591001) – All Subjects 12-15 years – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

<u>Population</u>	<u>Number of Subjects Exposed to BNT162b2 (30 µg)</u>	<u>Total Number of Vaccine Doses</u>
	<u>(N<sup>a</sup>=49)</u> <u>n<sup>b</sup></u>	
-		
<u>Subjects with any baseline comorbidity</u>	<u>11</u>	<u>15</u>
<u>Chronic Pulmonary Disease</u>	<u>6</u>	<u>8</u>
<u>Diabetes With/Without Chronic Complication</u>	<u>1</u>	<u>2</u>
<u>Obese</u>	<u>4</u>	<u>5</u>

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 ≥95<sup>th</sup> 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\_121

### 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. ~~Please refer to Module 1.4.4 for details (Module 5.3.5.1, Section 9.3.1 and Section 9.3.2).~~

#### 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 ~~(Please refer to Module 1.4.4 for location details).~~
- 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).

#### Exclusion criteria

The participants enrolled were 12 years of age and older; with the 12- to ~~≤46~~15-year-old cohort most recently being included in the protocol in October 2020. 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~~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~~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 Pfizer-BioNTech COVID-19 vaccine 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 Pfizer-BioNTech COVID-19 vaccine is not expected to differ in these subjects when properly administered.

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

Not applicable. At the DLP of 14 November 2020, Pfizer BioNTech COVID-19 vaccine had not been marketed in any country/region. It is not possible to determine with certainty the number of individuals who received Pfizer-BioNTech COVID-19 vaccine 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 Pfizer-BioNTech COVID-19 vaccine were shipped worldwide. The estimated cumulative number of shipped doses of Pfizer-BioNTech COVID-19 vaccine by region, are summarized in Table 22.

**Table 22. Cumulative Estimated Shipped Doses<sup>a</sup> of Pfizer-BioNTech COVID-19 Vaccine by Region Worldwide**

<u>Region/Country</u>	<u>Total Number of Shipped Doses</u>	<u>% of Doses</u>
<u>Europe</u>	<u>51,545,325</u>	<u>40.8%</u>
<u>European Union (27)</u>	<u>36,340,590</u>	<u>28.8%</u>
<u>European Free Trade Association (3)</u>	<u>5,138,25</u>	<u>0.4%</u>
<u>Switzerland</u>	<u>767,520</u>	<u>0.6%</u>
<u>UK</u>	<u>13,643,175</u>	<u>10.8%</u>
<u>Other Countries</u>	<u>280,215</u>	<u>0.2%</u>
<u>Commonwealth of Independent States<sup>b</sup></u>	<u>0</u>	<u>0.0%</u>
<u>North America</u>	<u>56,577,885</u>	<u>44.8%</u>
<u>US</u>	<u>54,326,415</u>	<u>43.0%</u>
<u>Canada</u>	<u>2,251,470</u>	<u>1.8%</u>
<u>Central and South America</u>	<u>2,965,170</u>	<u>2.3%</u>
<u>Asia</u>	<u>14,467,830</u>	<u>11.5%</u>
<u>Oceania</u>	<u>656,370</u>	<u>0.5%</u>
<u>Africa</u>	<u>0</u>	<u>0.0%</u>
<u>Total</u>	<u>126,212,580</u>	<u>100.0%</u>

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;

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## Method Used to Calculate Exposure

Not applicable.

## Exposure

Not applicable.

### 2.1.2.a.3. Regulatory Actions Related to Safety

~~Not applicable.~~

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 Pfizer-BioNTech COVID-19 vaccine in some special populations and no epidemiologic studies have been conducted in pregnant/lactating women, pediatric participants (<~~16~~12 years of age), and specific subpopulations that were excluded from the Pfizer-BioNTech COVID-19 vaccine program.

**Table 23. Exposure of Special Populations Included or not in Clinical Trial Development Programs**

Type of special population	Exposure
Pregnant women	<p>Available data on Pfizer-BioNTech COVID-19 vaccine administered to pregnant women are insufficient to inform on vaccine-associated risks in pregnancy. <del>Therefore, Pfizer BioNTech COVID-19 vaccine is not recommended for use during pregnancy.</del></p> <p><u>Participants 16 years of age and older</u></p> <p>Through the <del>DLP</del><u>cut-off date of 14 November 2020</u>, there were 11 cases (11 events) originating from Study C4591001, and all were unique pregnancies.</p> <p><u>Participants 12 to 15 years of age</u></p> <p><u>Through the cut-off date of 13 March 2021, there were no cases of pregnancies.</u></p>

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**Table 23. Exposure of Special Populations Included or not in Clinical Trial Development Programs**

Type of special population	Exposure
Breastfeeding women	<p>Breastfeeding women were not <u>initially</u> included in the Pfizer-BioNTech COVID-19 vaccine clinical development program.</p> <p>Data are not available to assess the effects of Pfizer-BioNTech COVID-19 vaccine on the breastfed infant or on milk production/excretion.</p> <p><u>Therefore, Pfizer-BioNTech COVID-19 vaccine is not recommended during breastfeeding.</u></p> <p>The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Pfizer-BioNTech COVID-19 vaccine and any potential adverse effects on the breastfed newborn infant/toddler from Pfizer-BioNTech COVID-19 vaccine or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptible to disease prevented by the vaccine.</p> <p><u>There Participants 16 years of age and older</u> <u>Through the cut-off date of 14 November 2020, there</u> were no CT cases indicative of exposure during breastfeeding.</p> <p>Women who were breastfeeding were excluded from study participation.</p> <p><u>Participants 12 to 15 years of age</u> <u>Through the cut-off date of 13 March 2021, there were no CT cases</u> <u>indicative of exposure during breastfeeding.</u></p>
<p>Participants with relevant comorbidities:</p> <ul style="list-style-type: none"> <li>• Participants with hepatic impairment</li> <li>• Participants with renal impairment</li> <li>• Participants with cardiovascular disease</li> <li>• Immunocompromised participants</li> <li>• Participants with a disease severity different from inclusion criteria in CTs</li> </ul>	<p>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 &gt;30 kg/m<sup>2</sup>, participants with stage 3 or worse chronic kidney disease, and participants with varying disease severity.</p> <p><u>Please refer to Table 14 for the exposure of special populations.</u></p> <p>Participants with potential immunodeficient status were not specifically included in the study population.</p> <p><u>Participants 16 years of age and older</u> <u>Please refer to Table 19 for the exposure of special populations.</u></p> <p><u>Participants 12 to 15 years of age</u> <u>Please refer to Table 20 and Table 21 for the exposure of special populations.</u></p>
Participants of different racial and/or ethnic origin	Please refer to Table 10 to Table 13 for exposure information by ethnic origin from the studies.
Subpopulations carrying known and relevant polymorphisms	No data available.

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**Table 23. Exposure of Special Populations Included or not in Clinical Trial Development Programs**

Type of special population	Exposure
Pediatric participants	<del>The Participants 12 to 15 years of age</del> <u>Emergency Use Authorization of Pfizer-BioNTech COVID-19 in adolescents 12 to 15 years of age is based on demonstration of safety, efficacy, and effectiveness. The effectiveness of the vaccine was demonstrated by comparison of the immune response in adolescents 12 to 15 years of age to participants 16 to 25 years of age.</u> <del>EUA of Pfizer-BioNTech COVID-19 vaccine does not include use in individuals younger than 16 12 years of age have not yet been established. Forty nine (49) children.</del> <u>One thousand a hundred eighty (1180) pediatric participants 12 to 15 years of age received Pfizer-BioNTech COVID-19 vaccine (Table 5 through the cut-off date of 13 March 2021 (Table 14 and Table 15).</u>
Elderly (≥65 years old)	<u>Participants 16 years of age and older</u> Clinical studies of Pfizer-BioNTech COVID-19 vaccine included 4580 participants 65 years of age and over. <del>Please refer to 2.1.2.a.1 Clinical Trial Exposure and Table 5, through the cut-off date of 14 November 2020 (Table 5).</del>

Abbreviations: EUA = emergency use authorization; BMI = body mass index; COVID-19 = coronavirus disease 2019; CT = clinical trial; ~~DLP = data lock point~~; ~~PVP = pharmacovigilance plan~~

### 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) ~~are not included in the list of safety concerns. For example, the determined adverse reactions: Injection site pain, Fever, Chills, Fatigue, Headache, Muscle pain, Joint pain and Lymphadenopathy (enlarged lymph nodes).~~
- 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 of vaccines that are known to healthcare professionals are not included in the list of safety concerns. ~~For example, anaphylactic reactions. Although the potential clinical consequences of an anaphylactic reaction are severe, this is a known risk of vaccines to healthcare professionals and patients, occurs with a very rare frequency, and is an acceptable potential risk in relation to the severity of the disease prevented.~~

## 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

Anaphylaxis

**Table 24. Anaphylaxis**

<b>Potential mechanisms, evidence source and strength of evidence</b>	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).																		
<p><b>Characterisation of the risk</b></p> <p><u>Participants 16 years of age and older</u></p> <p><u>Data from the CT database</u></p> <p>Information pertinent to the anaphylactic reactions observed in the ongoing Phase 3 clinical study C4591001 <u>through the cut-off date of 14 November 2020</u>, are summarized below:</p> <p>Two (2) serious events (Anaphylactic reaction and Anaphylactic shock) were reported. Anaphylactic reaction due to a bee sting in a <u>BNT162b2-Pfizer-BioNTech COVID-19 vaccine</u> recipient, and Anaphylactic shock due to an ant bite in a placebo recipient; both events were deemed not related to study treatment by the Investigator.</p> <p><u>Data from the safety database:</u></p> <p>Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 31 December 2020, the following numbers of potentially relevant cases were retrieved:</p> <ul style="list-style-type: none"> <li>824 cases [22.8 % of the total Post-marketing (PM) dataset], 1245 potentially relevant events, from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy.</li> </ul> <p>Overall event seriousness and outcome are summarized below.</p> <table border="1"> <thead> <tr> <th></th><th><b>Total Events N = 1245 (%)</b></th></tr> </thead> <tbody> <tr> <td>Serious events</td><td>314 (25.2)</td></tr> <tr> <td>Hospitalization</td><td>60 (4.8)</td></tr> <tr> <td colspan="2"><b>Distribution of events by Outcome<sup>a</sup></b></td></tr> <tr> <td>Outcome: Death</td><td>3 (0.2)</td></tr> <tr> <td>Outcome: Resolved/Resolving</td><td>603 (48.4)</td></tr> <tr> <td>Outcome: Not resolved</td><td>259 (20.8)</td></tr> <tr> <td>Outcome: Resolved with sequelae</td><td>31 (2.5)</td></tr> <tr> <td>Outcome: Unknown/No data</td><td>350 (28.1)</td></tr> </tbody> </table> <p>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 from the total number of events.</p> <ul style="list-style-type: none"> <li>43 cases (1.2 % of the total PM dataset), 43 relevant PTs, from the Anaphylactic reaction SMQ (Narrow) search strategy. The relevant PTs were: Anaphylactic reaction (32, 29 of which were serious), Anaphylactoid reaction (5, 4 of which were serious), Anaphylactic shock (4, 3 of which were serious), Circulatory collapse (1, serious), Shock symptom (1, serious).</li> </ul>			<b>Total Events N = 1245 (%)</b>	Serious events	314 (25.2)	Hospitalization	60 (4.8)	<b>Distribution of events by Outcome<sup>a</sup></b>		Outcome: Death	3 (0.2)	Outcome: Resolved/Resolving	603 (48.4)	Outcome: Not resolved	259 (20.8)	Outcome: Resolved with sequelae	31 (2.5)	Outcome: Unknown/No data	350 (28.1)
	<b>Total Events N = 1245 (%)</b>																		
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Outcome: Unknown/No data	350 (28.1)																		

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**Table 24. Anaphylaxis**

Overall event seriousness and outcome are summarized below.	
	<b>Total Events N = 43 (%)</b>
Serious events	38 (88.4)
Hospitalization	10 (23.3)
<b>Distribution of events by Outcome</b>	
Outcome: Death	0
Outcome: Resolved/Resolving	20 (46.5)
Outcome: Not resolved	3 (7)
Outcome: Resolved with sequelae	0
Outcome: Unknown/No data	20 (46.5)
<p><u>Participants 12 to 15 years of age</u></p> <p><u>Data from the CT database</u></p> <p><u>Anaphylactic reactions were not observed in the ongoing Phase 3 clinical study C4591001 in participants 12 to 15 years of age through the cut-off date of 13 March 2021.</u></p> <p><u>Data from the safety database:</u></p> <p><u>Through 28 February 2021, there were no cases reporting anaphylactic reactions<sup>a</sup> in the safety database in the 12 to 15 years of age participants.</u></p>	
<b>Risk factors and risk groups</b>	Known hypersensitivity to any components of the vaccine.
<b>Preventability</b>	Prevention of anaphylaxis may not be possible, particularly with the 1 <sup>st</sup> dose of a vaccine; therefore, healthcare professionals administering the vaccine must be vigilant for early signs and symptoms.
<b>Impact on the risk-benefit balance of the biologic product</b>	Anaphylactic reaction in an individual can be impactful (medically important) because it is a potentially life-threatening event requiring medical intervention.
<b>Public health impact</b>	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.

a. Search criteria have been reviewed compared to PVP version 0.3. The new search criteria are: Anaphylactic reaction SMO (Narrow and Broad, with the MedDRA algorithm applied), with relevant cases assessed according to Brighton Collaboration (BC) criteria.

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## Important Potential Risks

**Table 25. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)**

<b>Potential mechanisms, evidence source and strength of evidence</b>	<p>This potential risk is theoretical because it has not been described in association with the Pfizer-BioNTech COVID-19 vaccine 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.<sup>4,6</sup> 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.<sup>7</sup></p> <p>Potential mechanisms of enhanced disease may include both T cell-mediated [an immunopathological response favoring T helper cell type 2 (T<sub>H</sub>2) over T helper cell type 1 (T<sub>H</sub>1)] 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).<sup>8</sup></p>
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### Characterization of the risk

#### Participants 16 years of age and older

#### Data from the CT database

Confirmed Case of Postvaccination Severe COVID-19 – Safety Population (C4591001)				
Timing	BNT162b2 (30 µg) (N <sup>a</sup> =21721)		Placebo (N <sup>a</sup> =21729)	
	n <sup>b</sup> (%)	(95% CI) <sup>c</sup>	n <sup>b</sup> (%)	(95% CI) <sup>c</sup>
PD1 Before Dose 2	0	(0.0, 0.0)	4 (0.0)	(0.0, 0.0)
Within 7 days PD1	0	(0.0, 0.0)	0	(0.0, 0.0)
Within 14 days PD1	0	(0.0, 0.0)	3 (0.0)	(0.0, 0.0)
PD2	1 (0.0)	(0.0, 0.0)	5 (0.0)	(0.0, 0.1)
Within 7 days PD2	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Within 14 days PD2	0	(0.0, 0.0)	2 (0.0)	(0.0, 0.0)
Total <sup>d</sup>	1 (0.0)	(0.0, 0.0)	9 (0.0)	(0.0, 0.1)

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: 17NOV2020 (10:49) Source Data: adc19ef Table Generation: 19NOV2020 (00:22)  
(Cutoff date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: (CDISC)/C4591001\_RMP\_Phase1\_2\_3/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 cases in vaccinated individuals when

**Table 25. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)**

compared to those not vaccinated. It is challenging ~~if not impossible~~ 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 ~~needs to be~~ best performed at a population level,<sup>9</sup> as noted above. The table above shows a favorable balance of severe COVID-19 cases in participants receiving Pfizer-BioNTech COVID-19 vaccine versus those receiving placebo, providing reassurance against the potential risk of VAED/VAERD at this time.

Participants 12 to 15 years of age

Data from the CT database

There were no cases of VAED/VAERD as shown in the table below.

<b><u>Confirmed Case of Postvaccination Severe COVID-19 – All Subjects 12-15 Years – Blinded Placebo-Controlled Follow-up Period – Safety Population (C4591001)</u></b>				
<b><u>Timing</u></b>	<b><u>BNT162b2 (30 µg)</u></b>		<b><u>Placebo</u></b>	
	<b><u>(N<sup>a</sup>=1131)</u></b>		<b><u>(N<sup>a</sup>=1129)</u></b>	
	<b><u>n<sup>b</sup> (%)</u></b>	<b><u>(95% CI<sup>c</sup>)</u></b>	<b><u>n<sup>b</sup> (%)</u></b>	<b><u>(95% CI<sup>c</sup>)</u></b>
<b><u>PD1 Before Dose 2</u></b>	<b><u>0</u></b>	<b><u>(0.0, 0.3)</u></b>	<b><u>0</u></b>	<b><u>(0.0, 0.3)</u></b>
<b><u>Within 7 days PD1</u></b>	<b><u>0</u></b>	<b><u>(0.0, 0.3)</u></b>	<b><u>0</u></b>	<b><u>(0.0, 0.3)</u></b>
<b><u>PD2</u></b>	<b><u>0</u></b>	<b><u>(0.0, 0.3)</u></b>	<b><u>0</u></b>	<b><u>(0.0, 0.3)</u></b>
<b><u>Total<sup>d</sup></u></b>	<b><u>0</u></b>	<b><u>(0.0, 0.3)</u></b>	<b><u>0</u></b>	<b><u>(0.0, 0.3)</u></b>

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: 01APR2021 (19:34)  
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: /nda2\_unblinded/C4591001\_PVP\_BLA/adeff\_s901\_1215

Data from the safety database:

Through 28 February 2021, there were no cases reporting VAED including VAERD in the safety database in the 12 to 15 years of age participants.

<b>Risk factors and risk groups</b>	It is postulated that the potential risk may be increased in individuals producing lower neutralizing antibody titers or in those demonstrating waning immunity. <sup>8,9</sup>
<b>Preventability</b>	An effective vaccine against COVID-19 that produces high neutralizing titers and a T <sub>H</sub> 1 predominant CD4 <sup>+</sup> T cell response and strong CD8 <sup>+</sup> T cell response, is expected to mitigate the risk of VAED/VAERD; <sup>1,8</sup> that immune profile is elicited by <u>BNT162b2/Pfizer-BioNTech COVID-19 vaccine</u> in clinical and preclinical studies. <sup>10,11</sup>
<b>Impact on the risk-benefit balance of the biologic product</b>	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.
<b>Public health impact</b>	The potential risk of VAED/VAERD could have a public health impact if large populations of individuals are affected.

## 2.1.2.c.2.2. Presentation of Missing Information

**Table 26. 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 Pfizer-BioNTech COVID-19 vaccine 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 Pfizer-BioNTech COVID-19 vaccine are planned.

**Table 27. Vaccine Effectiveness**

Evidence source:

Although vaccine efficacy in a 3 controlled clinical studies is the objective of the pivotal study, real-world vaccine effectiveness when the Pfizer-BioNTech COVID-19 vaccine 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. Plans for Three post-authorization effectiveness in real-world use are being developed, planned: 1 non-interventional study (C4591014) and 2 low-interventional studies (W1235284 and W1255886) to determine the effectiveness of Pfizer-BioNTech COVID-19 vaccine when administered outside of the clinical setting.

**Table 28. Use in Paediatric Individuals <16<sup>12</sup> Years of Age<sup>a</sup>**

Evidence source:

Pfizer-BioNTech COVID-19 vaccine has not been studied in paediatric individuals younger than 12 years of age due to their exclusion from the pivotal clinical study; there are limited data for paediatric individuals aged between 12 and <16 years, recently included in Phase 3 of study C4591001. 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 limited data in individuals younger than 16<sup>12</sup> years of age is communicated in product labeling; a. A clinical study of the safety and immunogenicity of Pfizer-BioNTech COVID-19 vaccine in individuals between 12 and 15 years of age is ongoing (C4591001); 2 clinical studies of the safety, tolerability, immunogenicity and efficacy of Pfizer-BioNTech COVID-19 vaccine in individual individuals younger than 12 years (0 to <5 years of age and 5 to <[C4591007 (< 12 years of age) are planned]) is ongoing.

a. Missing information has been re-worded to reflect current state

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#### 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,<sup>3</sup> 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 Pfizer-BioNTech COVID-19 vaccine have not been done, therefore there is not sufficient data to understand the effect on vaccine effectiveness of Pfizer-BioNTech COVID-19 vaccine or co-administered vaccines. A co-administration study with seasonal influenza vaccine is planned. If Pfizer-BioNTech COVID-19 vaccine 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~~≥12 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.<sup>12</sup> 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.<sup>13</sup>

Estimates of SARS-CoV-2 incidence change rapidly. ~~As of 9 November 2020, the overall number of people who had been infected with SARS-CoV-2 was over 50 million worldwide. In the EU and the UK, the number of confirmed cases had accumulated to over 9 million people, corresponding to 337 per 100,000 people. Across countries in the EU, the number of confirmed cases ranged from 40 to 1,017 cases per 100,000 people. Slovakia, Greece and Hungary reported an incidence below 50 per 100,000 whereas Spain, Sweden and Luxembourg reported over 700 confirmed cases per 100,000 people. 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.~~<sup>14</sup>

As of 03 March 2021, the overall number of people who had been infected with SARS-CoV-2 was over 115 million worldwide,<sup>15</sup> an increase of nearly 100 million in the 7 months since 28 July 2020.<sup>16</sup> Table 29 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.<sup>15</sup>

In the US, the number of confirmed cases had reached over ~~1029~~ million cases (3,126(8,864 per 100,000 people) by ~~the beginning of November~~ 03 March 2021.<sup>15</sup> This is an increase from 4.5 million (1,357 per 100,000) by 28 July 2020.<sup>17</sup>

**Table 29. Incidence, Prevalence, and Mortality of COVID-19 as of 03 March 2021<sup>15</sup>**

-	Total Cases	Incidence: Total Cases/ 100,000	Active Cases <sup>a</sup>	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
<i>EU-27 Countries</i>							
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



**Table 29. Incidence, Prevalence, and Mortality of COVID-19 as of 03 March 2021<sup>15</sup>**

-	<u>Total Cases</u>	<u>Incidence: Total Cases/ 100,000</u>	<u>Active Cases<sup>a</sup></u>	<u>Prevalence: Active Cases/ 100,000</u>	<u>Total Deaths</u>	<u>Mortality: Deaths / 100,000</u>	<u>Population</u>
<u>Sweden</u>	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 varied 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.<sup>18</sup>

### 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 ~~9 November 2020~~ 03 March 2021, the overall prevalence for ~~the EU countries and UK (though not available for Sweden and the Netherlands)~~ was 37.01,398 active cases per 100,000.<sup>15</sup> compared to 51 per 100,000 on 28 July 2020.<sup>16</sup> The range of reported prevalence was 2.881 to 337.76,019 per 100,000 with Finland, Estonia and Hungary at the low end and Portugal, Luxembourg, Croatia, Denmark, and Germany reported the lowest prevalence while Belgium at the high end., France and Ireland reported the highest (Table 29).

In the US, the prevalence on ~~the same date~~ 03 March 2021 was similar to nearly twice as high as the combined EU+UK estimates, with 31.52,685 active cases per 100,000.<sup>14,15</sup> The prevalence in the US was 653 per 100,000 on 28 July 2020.<sup>16</sup>

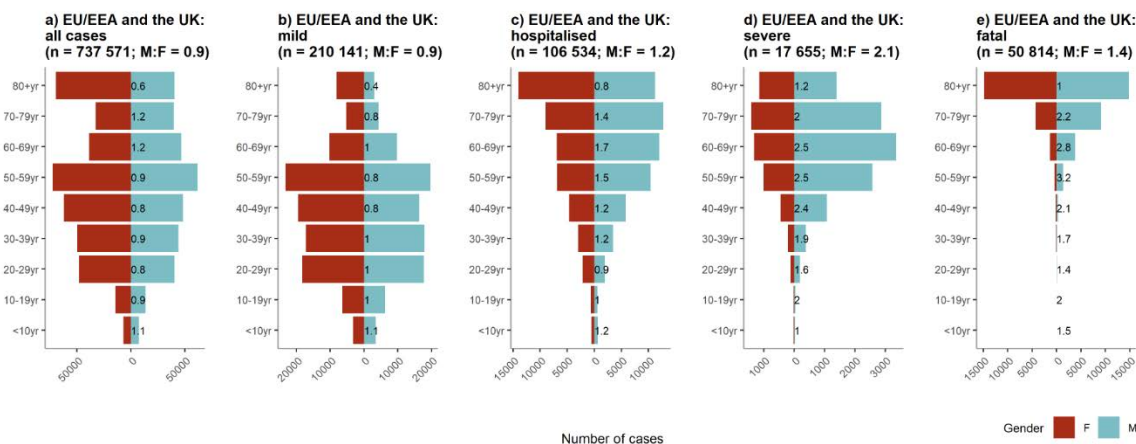
### Demographics of the population in the proposed indication and risk factors for the disease:

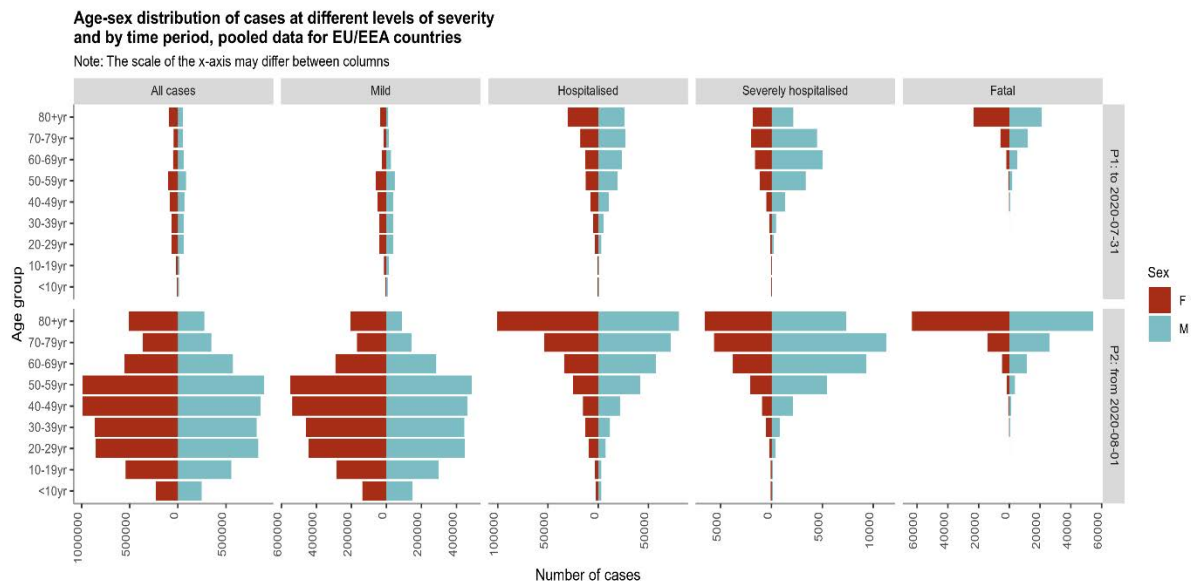
~~While anyone can become infected with SARS-CoV-2, symptoms of COVID-19 disease can range from very mild (or no symptoms) to severe. Risk factors for developing severe disease, include age over 60 years, male sex, diabetes, severe obesity, chronic kidney disease and congestive heart failure.<sup>19,20,21,22</sup>~~

~~The ECDC has since~~ 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 ~~their~~ the ECDC's TESSy database ~~TESSy~~, COVID-19 case-based data, including age and gender, are available for approximately 40 over 80% of the official number of cases reported by ECDC epidemic intelligence.<sup>23</sup> ~~All countries included in EU/EEA and UK, except Spain, Slovenia and Liechtenstein, have at some point during the pandemic provided case-based data to TESSy.<sup>24</sup>~~ 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.<sup>25</sup>

According to TESSy case-based data, accessed 7 ending on 31 July 2020 and the bottom half presents data from 01 August 2020, to 04 March 2021 (Figure 1), the). 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. However, males and older age groups are over-represented among the more severe cases (defined as hospitalized, severe, or fatal). Few cases were 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 data 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.<sup>19</sup> The distribution of age was different in the period of January–May. Those with severe outcomes (hospitalized, severely hospitalized, or fatal) have been disproportionately older and male compared to June–July. Between January and May 2020, 40% 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 were  $\geq 60$  years old and the largest proportion (18.7%) of cases were reported have increased dramatically in the 50–59 years age group. In contrast, between June and July, persons aged  $\geq 60$  years accounted for 17.3% of cases and the largest proportion (19.5%) of cases were reported in the 20–29 year age group.<sup>26</sup> 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 07 August 2020<sup>a</sup> 04 March 2021<sup>a</sup>**





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 31, 2020. 7 August 2020-8, 2021. 4 March 2021. "2.2 Age-sex pyramids"<sup>27</sup>, Accessed 6 March 2021<sup>25</sup>

In the US, surveillance data collected between 22 January 2020 and 30 May 2020 showed a similar age distribution of infected cases in both genders (Table 21). Among 1,320,488 laboratory confirmed COVID-19 cases, overall incidence per 100,000 persons was higher among individuals aged 40–49 years (541.6) and 50–59 years (550.5) than among those aged 60–69 years (478.4) and 70–79 years (464.2). Estimates were highest among persons aged ≥80 years (902.0) and lowest among children aged ≤9 years (51.1).<sup>28</sup> During June–August, the COVID-19 pandemic in the US affected a larger proportion of younger persons than during January–May 2020. In this period, incidence was highest in persons aged 20–29 years, accounting for >20% of all confirmed cases. The shift toward younger ages occurred in all four U.S. Census regions, regardless of changes in incidence during this period, and was reflected in COVID-19-like illness-related ED visits, positive SARS-CoV-2 RT-PCR test results, and confirmed COVID-19 cases.<sup>29</sup>

Of the 599,636 (45%) cases with information on both race and ethnicity in US surveillance data collected between 22 January 2020 and 30 May 2020, 36% were non-Hispanic white, 33% were Hispanic, 22% were black, 4% were non-Hispanic Asian, 4% were non-Hispanic, other or multiple race, 1.3% were American Indian/Alaskan Native, and <1% were non-Hispanic Native Hawaiian or other Pacific Islander.<sup>22</sup> An increased rate ratio of COVID-19 cases and hospitalization compared to White, non-Hispanic has been reported for all other race and ethnicity groups, underlying factors including socioeconomic status, access to health care and occupations are likely to be the actual risk factors.<sup>30</sup>

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 30.<sup>31</sup> 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 30. ~~Distribution and Estimated Cumulative Incidence of Reported Laboratory Confirmed COVID-19 Cases, by Sex and Age Group—United States, 22 January—30 May 2020<sup>a</sup>. 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<sup>31,a</sup>~~**

Event	Age group (years) Group	Proportion (%) Age	Cumulative Incidence % Sex	Proportion (%) Sex	Cumulative Incidence* Race <sup>b</sup>	Race %	Age Group	Age x Sex %	
								Males	Females
Cases	0-4	2	Males	47.8	H/L	12.7	0-4	49.5	48.3
	5-17	13.4	Females	121.4	AI/AN	1.2	5-17	49.8	50.2
	18-29	13.3		14.3	Asian	4.3	18-29	47.1	52.9
	30-39	16.8			Black	12.2	30-39	48.2	51.8
	40-49	17.0			NH/PI	0.4	40-49	53.6	52.3
	50-64	18.4		17.3	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	526.9	Males	54.3	H/L	12.7	0-4	43.4	52.4
	5-17	513.7	Females	74.5	AI/AN	1	5-17	42.2	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
	50-64	14.5			White	63.1	50-64	65	35
	65-74	21.3			M/O	64.4	65-74	10.8	940.0
	75-84	27.7					75-84	55.8	44.2
	85+	32.1					85+	41.8	58.2

a. ~~Data from Stokes.<sup>22</sup>~~

\* ~~Per 100,000 people~~ ~~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.<sup>32</sup> 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.<sup>15,17,25,34,35,36,37</sup> The majority (approximately 60%) of COVID-19 patients admitted to hospitals in the US have been male.<sup>15,17,25,34,35,36,37</sup> ~~African American COVID-19 patients have been reported to have an~~

increased risk of hospitalization<sup>45,26</sup> and mortality,<sup>38</sup> compared to white patients in the United States.<sup>33,39,40,41,42</sup>

African American COVID-19 patients have been reported to have an increased risk of hospitalization<sup>39,43</sup> and mortality,<sup>44</sup> 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.<sup>45</sup> 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.<sup>46</sup> 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.<sup>47</sup> 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.<sup>48</sup> 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.<sup>48,49,50</sup> 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 31).<sup>51</sup> Risk of infection is also higher among some ethnic minority groups.<sup>52,53</sup>

**Table 31. Risk for COVID-19 Infection, Hospitalization, and Death by Age Group<sup>51</sup> and by Race/Ethnicity<sup>52</sup>**

<u>Age Group (years)</u>	<u>Rate ratios</u>		
	<u>Cases</u>	<u>Hospitalization</u>	<u>Death</u>
<u>0-4</u>	<u>&lt;1</u>	<u>2</u>	<u>2</u>
<u>5-17<sup>a</sup></u>	<u>1</u>	<u>1</u>	<u>1</u>
<u>18-29</u>	<u>3</u>	<u>7</u>	<u>15</u>
<u>30-39</u>	<u>2</u>	<u>10</u>	<u>45</u>
<u>40-49</u>	<u>2</u>	<u>15</u>	<u>130</u>
<u>50-64</u>	<u>2</u>	<u>25</u>	<u>400</u>
<u>65-74</u>	<u>2</u>	<u>35</u>	<u>1100</u>
<u>75-84</u>	<u>2</u>	<u>55</u>	<u>2800</u>



<u>85+</u>	<u>2</u>	<u>80</u>	<u>7900</u>
<b><u>Race/Ethnicity</u></b>			
<u>Non-Hispanic White</u> <sup>b</sup>	<u>1</u>	<u>1</u>	<u>1</u>
<u>American Indian or Alaska Native, non-Hispanic</u>	<u>1.9</u>	<u>3.7</u>	<u>2.4</u>
<u>Asian, non-Hispanic</u>	<u>0.7</u>	<u>1.1</u>	<u>1.0</u>
<u>Black or African American, non-Hispanic</u>	<u>1.1</u>	<u>2.9</u>	<u>1.9</u>
<u>Hispanic or Latino</u>	<u>1.3</u>	<u>3.2</u>	<u>2.3</u>

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.<sup>51,52,53,54,55,56</sup> Risks of hospitalization and death increase dramatically for every 10-year age group above age 17 (Table 31).<sup>51,56</sup> Table 31 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.<sup>52</sup>

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.<sup>53,55,56,57</sup> 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.<sup>58</sup>

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.<sup>53,54,55,56,57</sup> Table 32 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.<sup>56</sup>

**Table 32. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death<sup>56</sup>**

<u>Characteristic</u>	<u>Category</u>	<u>COVID-19 death Hazard Ratio</u>	
		<u>Adjusted for age and sex</u>	<u>Fully adjusted</u>
<u>Age</u>	<u>18-39</u>	<u>0.05 (0.04-0.07)</u>	<u>0.06 (0.04-0.08)</u>
	<u>40-49</u>	<u>0.28 (0.23-0.33)</u>	<u>0.30 (0.25 - 0.36)</u>
	<u>50-59</u>	<u>1.00 (ref)</u>	<u>1.00 (ref)</u>
	<u>60-69</u>	<u>2.79 (2.52-3.10)</u>	<u>2.40 (2.16-2.66)</u>

**Table 32. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death<sup>56</sup>**

<u>Characteristic</u>	<u>Category</u>	<u>COVID-19 death Hazard Ratio</u>	
		<u>Adjusted for age and sex</u>	<u>Fully adjusted</u>
	<u>70-79</u>	<u>8.62 (7.84-9.46)</u>	<u>6.07 (5.51-6.69)</u>
	<u>80+</u>	<u>38.29 (35.02-41.87)</u>	<u>20.60 (18.70-22.68)</u>
<u>Sex</u>	<u>Female</u>	<u>1.00 (ref)</u>	<u>1.00 (ref)</u>
	<u>Male</u>	<u>1.78 (1.71-1.85)</u>	<u>1.59 (1.53-1.65)</u>
<u>BMI (kg/m<sup>2</sup>)</u>	<u>Not obese</u>	<u>1.00 (ref)</u>	<u>1.00 (ref)</u>
	<u>30-34.9 (obese class I)</u>	<u>1.23 (1.17-1.30)</u>	<u>1.05 (1.00-1.11)</u>
	<u>35-39.9 (obese class II)</u>	<u>1.81 (1.68-1.95)</u>	<u>1.40 (1.30-1.52)</u>
	<u>40+ (obese class III)</u>	<u>2.66 (2.39-2.95)</u>	<u>1.92 (1.72-2.13)</u>
<u>Smoking</u>	<u>Never</u>	<u>1.00 (ref)</u>	<u>1.00 (ref)</u>
	<u>Former</u>	<u>1.43 (1.37-1.49)</u>	<u>1.19 (1.14-1.24)</u>
	<u>Current</u>	<u>1.14 (1.05-1.23)</u>	<u>0.89 (0.82-0.97)</u>
<u>Ethnicity<sup>a</sup></u>	<u>White</u>	<u>1.00 (ref)</u>	<u>1.00 (ref)</u>
	<u>Mixed</u>	<u>1.62 (1.26-2.08)</u>	<u>1.43 (1.11-1.84)</u>
	<u>South Asian</u>	<u>1.69 (1.54-1.84)</u>	<u>1.45 (1.32-1.58)</u>
	<u>Black</u>	<u>1.88 (1.65-2.14)</u>	<u>1.48 (1.29-1.69)</u>
	<u>Other</u>	<u>1.37 (1.13-1.65)</u>	<u>1.33 (1.10-1.61)</u>
<u>IMD quintile<sup>c</sup></u>	<u>1 (least deprived)</u>	<u>1.00 (ref)</u>	<u>1.00 (ref)</u>
	<u>2</u>	<u>1.16 (1.08-1.23)</u>	<u>1.12 (1.05-1.19)</u>
	<u>3</u>	<u>1.31 (1.23-1.40)</u>	<u>1.22 (1.15-1.30)</u>
	<u>4</u>	<u>1.69 (1.59-1.79)</u>	<u>1.51 (1.42-1.61)</u>
	<u>5 (most deprived)</u>	<u>2.11 (1.98-2.25)</u>	<u>1.79 (1.68-1.91)</u>
<u>Blood pressure</u>	<u>Normal</u>	<u>1.00 (ref)</u>	<u>1.00 (ref)</u>
	<u>High BP or diagnosed hypertension</u>	<u>1.09 (1.05-1.14)</u>	<u>0.89 (0.85-0.93)</u>
<u>Respiratory disease excluding asthma</u>		<u>1.95 (1.86-2.04)</u>	<u>1.63 (1.55-1.71)</u>
<u>Asthma<sup>b</sup> (vs. none)</u>	<u>With no recent OCS use</u>	<u>1.13 (1.07-1.20)</u>	<u>0.99 (0.93-1.05)</u>
	<u>With recent OCS use</u>	<u>1.55 (1.39-1.73)</u>	<u>1.13 (1.01-1.26)</u>
<u>Chronic heart disease</u>		<u>1.57 (1.51-1.64)</u>	<u>1.17 (1.12-1.22)</u>
<u>Diabetes<sup>c</sup> (vs. none)</u>	<u>With HbA1c &lt; 58 mmol/mol</u>	<u>1.58 (1.51-1.66)</u>	<u>1.31 (1.24-1.37)</u>
	<u>With HbA1c ≥ 58 mmol/mol</u>	<u>2.61 (2.46-2.77)</u>	<u>1.95 (1.83-2.08)</u>
	<u>With no recent HbA1c measure</u>	<u>2.27 (2.06-2.50)</u>	<u>1.90 (1.72-2.09)</u>

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**Table 32. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death<sup>56</sup>**

Characteristic	Category	COVID-19 death Hazard Ratio	
		Adjusted for age and sex	Fully adjusted
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 <sup>d</sup> (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<sup>-1</sup> per 1.73 m<sup>2</sup> 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:

~~At the DLP (14 November 2020) of this PVP, there were no~~ Through 28 February 2021, other approved COVID-19 vaccines were authorized and recommended for active immunization against COVID-19. ~~At the time that this vaccine was use in advanced development there were other vaccines in similar late phase development, the United States including vaccines from Moderna (NCT04470427), Sinovac (NCT04456595), AstraZeneca (NCT04516746), and and Johnson & Johnson/Janssen (NCT04505722), which).~~ Others may subsequently be approved, ~~as may others in earlier development.~~

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

~~The natural history of COVID-19 disease is not yet fully understood. In the US, 14% of individuals testing positive for SARS-CoV-2 22 January–30 May 2020 were reported to require hospitalization. The rate was lowest (<9%) among age groups <50 years, and highest among those older than 70 years (33%) and among patients with underlying health conditions (45.4%).<sup>22</sup>~~

~~Based on rates of severe disease reported in mainland China and assuming severe cases would be hospitalized, a demography-adjusted and under ascertainment-adjusted model~~



~~estimated the proportion of infected individuals requiring hospitalization. The proportions ranged from 8.2% in the age group 50-59 years to 18.4% in those older than 80 years. In the age groups below 50 years, less than 5% of infections were estimated to lead to hospitalization.<sup>59</sup>~~

### *Symptoms of COVID-19*

The clinical manifestations of COVID-19 vary widely, from asymptomatic infection in 17-20%,<sup>60,61</sup> to critical illness and death. The most common symptoms of COVID-19 are fever, cough, and shortness of breath (Table 33).<sup>62</sup>

**Table 33. Signs and symptoms among 291 pediatric (age <18 years) and 10,944 adult (age 18–64 years) patients<sup>a</sup> with laboratory confirmed COVID-19 — United States, February 12–April 2, 2020<sup>62</sup>**

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

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.<sup>63,64</sup> 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.<sup>64</sup> 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.<sup>63</sup>

### **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.<sup>65</sup> 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.<sup>66</sup>

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%).<sup>67,68,69,70</sup> Approximately 17% to 40% of those hospitalized with COVID-19

experience severe symptoms necessitating intensive care.<sup>16,33,48,43,2667</sup> More than 75% of patients hospitalized with COVID-19 require supplemental oxygen.<sup>16,71</sup> ~~The most common symptoms<sup>72</sup>~~

~~Studies early in hospitalized 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.<sup>63</sup> In 17 countries of the EU/EEA with available data, 1.8 patients are fever (up to 90% per 100,000 population were in the ICU due to COVID-19 for the week ending 28 February 2021.<sup>66</sup> A recent meta-analysis found that, of patients), dry cough (60%–86%), shortness of breath (53%–80%), fatigue (38%), nausea/vomiting <19 years of age, 11% went to the ICU, non-invasive ventilation was administered among 12%, and 4% required mechanical ventilation.<sup>61</sup>~~

### 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).<sup>65</sup> 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).<sup>73</sup> 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).<sup>74</sup> According to a recent meta-analysis of pediatric studies published through October 2020, the mortality for patients <19 years of age is 2%.<sup>61</sup>~~

~~Mortality data are also presented from Worldometer, an independent organization that publishes current, reliable COVID-19 statistics online.<sup>17</sup> 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 diarrhea (15%–39%), and myalgia (15%–44%).<sup>18,25,28,32,75,76</sup>–132 per 100,000 people. Reported mortality among EU countries and the UK ranged from 14 to 195 deaths per 100,000 (Table 29). Finland and Cyprus reported the lowest mortality; Czech Republic, Belgium and Slovenia reported the highest.<sup>15</sup>~~

~~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.<sup>15</sup>~~

~~Overall reported mortality among hospitalized COVID-19 patients varies from 12.8% to 26% in the EU and UK.<sup>43,45,77,78</sup> Mortality rates are declining over time, presumably due to an improved understanding of COVID-19 and its management.<sup>77,79</sup>~~

### Complications of COVID-19 and Long-COVID

~~Complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney, and coagulation system.<sup>26,28,32</sup> Venous and arterial thromboembolic events occur in 10% to 25% in hospitalized patients with COVID-19 and in the ICU, venous and arterial thromboembolic events may occur in up to 31% to 59% of patients.<sup>22,33,40,70</sup> 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.<sup>80</sup>~~

As of 28 July 2020, the total number of COVID-19 related deaths in the EU and UK was over 100,000 and, in the US more than 150,000 people had died from COVID-19.<sup>14</sup> Overall reported mortality among hospitalized COVID-19 patients varies from 12.8% to 26% in Europe<sup>16,34,81</sup> and 20%–23% in the US.<sup>18,26,28</sup> In the US, studies have also reported up to 40% mortality in patients admitted to the ICU.<sup>25,26,28</sup> Age older than 60 years, male sex, hypertension, cardiovascular disease and chronic pulmonary disease, have been shown to be independently associated with in-hospital death of COVID-19 patients.<sup>18,25,35</sup>

COVID-19 symptoms can persist weeks or months beyond the acute infection.<sup>82,83</sup> 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).<sup>84</sup>

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-/perimy-/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%).<sup>85</sup> 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.<sup>86,87,61</sup>

### 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.<sup>18,39,22,25,40,27,41,67,28,29,32,70</sup> 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 34 below.

**Table 34. Preconditions among COVID-19 Patients in EU/EEA and UK, by Severity of Disease.**  
Case-based Data from TESSy Produced ~~on 24 September 2020~~ 04 March 2021

Precondition	EU/EEA, produced on 04 March 2021			
	Mild % (N=66,257)	Hospitalized % (N=48,494) Hosp	Severe	Fatal % (N=12,796)
Total N	1,155,969	214,784	35,468	67,011
Asplenia (%)	0	0	0	0
Asthma (%)	10.5	31.6	43.1	1.6
Cancer, malignancy (%)	42.1	54.7	9.7	9.3
Cardiac disorder, excluding hypertension (%)	396.2	12118.4	16120.7	24.7
Chronic lung disease, excluding asthma (%)	1.8	4.7	5.3	65.3

**Table 34. Preconditions among COVID-19 Patients in EU/EEA and UK, by Severity of Disease.**  
**Case-based Data from TESSy Produced on 24 September 2020** **04 March 2021**

Precondition	EU/EEA, produced on 04 March 2021			
	Mild % (N=66,257)	Hospitalized % (N=48,494) Hosp	Severe	Fatal % (N=12,796)
Current smoking (%)	2.40.9	0.3	0.34	0.1
Diabetes (%)	2.83.3	13.9	18.9	11.5.6
Haematological disorders (%)	0	0.43	0.71	0.62
HIV/other immune deficiency (%)	0.51	0.9	1.6	4.0.8
Hypertension (%)	2.20.7	3.9.0	18.4	6.3
Kidney-related condition, renal disease (%)	0.63	4.12.3	8.12.2	3.7
Liver-related condition, liver disease (%)	0.32	1.60.7	4.0.7	0.6
Neuromuscular disorder, chronic neurological (%)	0.6	2.4	1.36	7.1.2
Obesity (%)	0.62	0.32	0.14	0.2
Other endocrine disorder, excluding diabetes (%)	0.4	0.2	0.31	0.21
Rheumatic diseases including arthritis (%)	0	0.1	0	0
Tuberculosis (%)	0	0	0	0
None (%)	79.382.5	41.242.8	12.432.7	27.3

Abbreviation: Hosp = Hospitalized

Table 35 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.<sup>53</sup> 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 35. 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<sup>53</sup>**

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

**Table 35. 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<sup>53</sup>**

<u>Comorbidity</u>	<u>Tested</u> (N= 629,953) <u>%</u>	<u>Positive</u> (N= 54,645) <u>%</u>	<u>Hospitalized</u> (N= 8,536) <u>%</u>
<u>Coronary Artery Disease</u>	<u>5.5</u>	<u>3.6</u>	<u>9.7</u>
<u>Myocardial Infarction</u>	<u>2.2</u>	<u>1.6</u>	<u>5.5</u>
<u>Congestive Heart Failure</u>	<u>5.3</u>	<u>3.9</u>	<u>13.2</u>
<u>Kidney Disease</u>	<u>5.6</u>	<u>5.3</u>	<u>17.2</u>
<u>Liver Disease</u>	<u>3.1</u>	<u>2.5</u>	<u>4.0</u>
<u>Cancer</u>	<u>6.1</u>	<u>3.0</u>	<u>6.3</u>

### 2.1.2.f. Pharmacological Class Effects

There are ~~no other~~ 2 vaccines ~~with a mRNA platform that have been approved by competent authorities because it is a new class of vaccines. At this time there are no known safety issues in humans that are specifically related to the mRNA platform such as the one utilized in (including Pfizer-BioNTech COVID-19 vaccine-) with a mRNA platform authorized for emergency use in multiple jurisdictions since 11 December 2020.~~ Theoretical concerns ~~that have been considered 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. ~~system-~~ 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.<sup>88,89</sup> 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 36. Ongoing Safety Concerns**

Important Identified Risks	Anaphylaxis
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 <del>paediatric</del> <u>pediatric</u> individuals < <del>16</del> <u>12</u> years of age <sup>a</sup>

a. Missing information has been re-worded to reflect current state



### 3.1.2. Routine Pharmacovigilance Practices

- Routine pharmacovigilance is a critical component of activities relating to the detection, assessment, understanding and prevention of AEs. 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 MAH, 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 MAH, 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 mRNA 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 mRNA 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 37. Action Plan for Important Identified Risk “Anaphylaxis”**

Actions proposed	<ul style="list-style-type: none"> <li>• Communication of this important identified risk via label (Sections 4 - <i>Contraindications</i>, 5.1 - <i>Management of Acute Allergic Reactions</i> and 6- <del><i>Overall Safety Summary</i></del>, 2 - <i>Post Authorization Experience</i>).</li> <li>• 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.</li> <li>• <del>C4591011- Safety Surveillance</del> C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the <u>United States</u>.</li> <li>• <del>C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 vaccine in the</del> US Department of Defense <del>Population</del> <u>population</u> following <del>emergency use authorization</del> <u>Emergency Use Authorization</u>.</li> <li>• C4591012-; Post-emergency use authorization active <u>safety surveillance of adverse events of special interest (AESI) study</u> among individuals in the Veteran’s Affairs Health System receiving Pfizer--BioNTech <u>Coronavirus Disease 2019 (COVID-19)</u> vaccine.</li> </ul>
Objective of proposed actions	<ul style="list-style-type: none"> <li>• Labelling communicates the risk of anaphylaxis.</li> <li>• C4591001: To evaluate the safety, tolerability, immunogenicity, and efficacy of Pfizer-BioNTech COVID-19 vaccine. 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.</li> <li>• <del>C4591011: Assessment of</del> C4591009: To assess the occurrence of safety events of interest, <del>including severe or atypical, in the general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 in a cohort of people within the Department of Defense Healthcare selected data sources participating in the US Sentinel System.</del></li> <li>• <del>C4591012: Assessment of occurrence</del> C4591011: To assess whether individuals in the US DoD Military Health System (MHS) experience <u>increased risk</u> of safety events of interest, <del>including severe or atypical following receipt of the Pfizer-BioNTech COVID-19 in real world use vaccine.</del></li> <li>• 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 Pfizer-BioNTech COVID-19 mRNA vaccine.</li> </ul>

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**Table 37. Action Plan for Important Identified Risk “Anaphylaxis”**

Rationale for proposed actions	<ul style="list-style-type: none"> <li>• Labeling communicates to health care provider the risk of anaphylaxis.</li> <li>• C4591001: Long-term monitoring throughout the clinical study for up to 2 years to assess the risk for vaccine-associated enhanced disease.</li> <li>• <u>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.</u></li> <li>• C4591011 and C4591012: Robust <del>and long-term</del> 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 <u>Pfizer-BioNTech COVID-19</u> vaccine under an <u>Emergency Use Authorization (EUA)</u>.</li> </ul>
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**Table 37. Action Plan for Important Identified Risk “Anaphylaxis”**

Monitoring by the sponsor for safety issue and proposed actions	<ul style="list-style-type: none"> <li>• C4591001: Safety evaluations will include <u>AEs of Special Interest/AESI</u>, including anaphylaxis; these will be collected systemically and monitored throughout the Phase 3 study.</li> <li>• <u>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 anaphylaxis, 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 anaphylaxis, as well as selected pregnancy-related and birth outcomes.</u></li> <li>• C4591011 and C4591012: <ol style="list-style-type: none"> <li>1. The collection of safety data in vaccine recipients is critical to our understanding of the vaccine safety profile and to enable <u>efficient</u> safety signal detection and, if needed, further risk mitigation during <u>an</u> 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. <u>Please refer to the EUA Safety Surveillance Study Plan in Attachment 1 (Safety Surveillance Plan) for details on the proposed activities.</u></li> <li>2. <u>Long-term, active</u> <u>Active</u> 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. <u>Availability of Pfizer-BioNTech COVID-19 vaccine through an EUA provide the earliest opportunity to initiate these studies.</u> Pfizer-BioNTech plans to conduct active surveillance studies of individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine under <u>an</u> EUA in populations <u>expected to be eligible/prioritized</u> in the early stages of the EUA, <u>eg, healthcare workers and e.g., active military and elderly</u>, as described in <u>Attachment 3 (the study protocols C4591011 draft protocol) and Attachment 4 (C4591012 draft protocol).</u> <u>As feasible, additional populations will be sought for inclusion as vaccine roll-out staging expands, submitted to FDA on 29 January 2021.</u> The study period will be <u>approximately 30 months</u> following a availability of vaccine under EUA <u>in target populations</u>. The studies will capture hospitalizations, deaths and serious safety events of interest, including anaphylaxis.</li> </ol> </li> </ul>
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**Table 37. Action Plan for Important Identified Risk “Anaphylaxis”**

Milestones for evaluation and reporting	<ul style="list-style-type: none"> <li>• C4591001 (ongoing Study): <ul style="list-style-type: none"> <li>• <del>Protocol submission: 22 April 2020 (Initial version); 30 October 2020 (Amendment No. 9)</del></li> <li>• <del>CSR submission on completion of the first efficacy IA with 94 cases: 12 November 2020;</del></li> <li>• <del>CSR submission on completion of full efficacy analysis with 164 cases: November 2020;</del></li> <li>• CSR submission upon regulatory request: at any time.</li> <li>• CSR submission 6 months post Dose 2: 31 <del>December</del> May 2021;</li> <li>• Final CSR submission with supplemental follow-up: 31 August 2023.</li> </ul> </li> <li>• C4591009: <ul style="list-style-type: none"> <li>• <u>Protocol submission: 31 August 2021</u></li> <li>• <u>Monitoring report submission: 31 October 2022</u></li> <li>• <u>Interim Analysis submission: 31 October 2023</u></li> <li>• <u>Final study report submission: 31 October 2025.</u></li> </ul> </li> <li>• C4591011 and C4591012: <ul style="list-style-type: none"> <li>• Interim study reports will be <del>generated</del> <u>submitted on the following dates based</u> on data collected <del>within the following study periods</del> post-EUA <del>vaccination</del> in target populations: <ul style="list-style-type: none"> <li><del>31 March 2021</del></li> <li>– 30 June 2021</li> <li>– 31 December 2021</li> <li>– 30 June 2022</li> <li>– 31 December 2022</li> </ul> </li> <li>• <del>Reports will be submitted within 1 month of end of interim study period.</del></li> <li>• Final study reports will be <del>based on a study period of 30 months and submitted within 6 months of end of study</del> <u>submitted by 31 December 2023.</u></li> </ul> </li> </ul>
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## Action Plan for Important Potential Risks

**Table 38. Action Plan for Important Potential Risk “Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)”**

Actions proposed	<ul style="list-style-type: none"> <li>• 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.</li> <li>• C4591008-; <u>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</u></li> <li>• C4591011-; <u>Active safety surveillance of the Pfizer-BioNTech COVID-19 vaccine in the US Department of Defense population following Emergency Use Authorization.</u></li> <li>• C4591012- <u>Three post-; Post-emergency use authorization epidemiological safety studies, encompassing primary and secondary data collection to perform long-term active safety surveillance for safety events of interest, including severe or atypical COVID-19 disease, study among individuals vaccinated with in the Veteran’s Affairs Health System receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) vaccine.</u></li> <li>• <u>C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States.</u></li> </ul>
Objective of proposed actions	<ul style="list-style-type: none"> <li>• <del>The objective of the C4591001 study is;</del> to evaluate the safety, tolerability, immunogenicity, and efficacy of Pfizer-BioNTech COVID-19 vaccine. <del>Further, an</del> <u>An</u> 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.</li> <li>• C4591008, <u>C4591009</u>, C4591011, and C4591012- <del>The objective of the 3 epidemiological post authorization safety studies is;</del> 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 Pfizer-BioNTech COVID-19 vaccine <u>under a</u> <del>since</del> <u>since</u> EUA.</li> </ul>
Rationale for proposed actions	<ul style="list-style-type: none"> <li>• C4591001: Robust and long-term monitoring throughout the clinical study for up to 2 years to assess the risk for vaccine-associated enhanced disease.</li> <li>• C4591008, <u>C4591009</u>, C4591011 and C4591012-; Robust <del>and long term</del> 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 <u>under an EUA, in the early stages of an EUA as well as with broader vaccination roll-out.</u></li> </ul>
Monitoring by the sponsor for safety issue and proposed actions	<ul style="list-style-type: none"> <li>• C4591001: Protocol prespecified stopping and alert rules were set for detecting enhanced COVID-19. 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 a diverse 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-</li> </ul>

**Table 38. Action Plan for Important Potential Risk “Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)”**

<p><u>Monitoring by the sponsor for safety issue and proposed actions (Cont'd)</u></p>	<p>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.</p> <p>Additional safety evaluations will include <u>AEs of Special Interest (AESI)</u> that could represent symptoms of severe COVID-19 disease; these will be collected systemically and monitored throughout the Phase 3 study.</p> <p><u>1. C4591008, C4591009, C4591011, C4591012:</u> 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 <del>an</del><u>the</u> 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. <u>Please refer to the EUA Safety Surveillance Study Plan in Attachment 1 (Safety Surveillance Plan) for details on the proposed activities.</u></p> <ul style="list-style-type: none"> <li>• <u>Long term, active</u> <u>Active</u> 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. <u>Availability of Pfizer BioNTech COVID-19 vaccine through an EUA provide the earliest opportunity to initiate these studies.</u> Pfizer-BioNTech plans to conduct active surveillance studies of <u>vaccinated</u> individuals <u>vaccinated with the Pfizer BioNTech COVID-19 vaccine under EUA</u> in populations <u>expected to be eligible/prioritized</u> in the early stages of the EUA, <u>eg, e.g.,</u> healthcare workers <u>and</u>, active military, <u>and elderly</u>, as described in <u>Attachment 2 (C4591008 draft protocol); Attachment 3 (submitted to FDA on 28 January 2021; C4591011 draft protocol); submitted to FDA on 29 January 2021 and Attachment 4 (C4591012 draft protocol).</u> <u>As feasible, additional populations will be sought for inclusion as vaccine roll-out staging expands, submitted to FDA on 29 January 2021.</u> The study period will be <u>approximately</u> 30 months following a availability of vaccine under EUA <u>in target populations</u>. 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).</li> <li>• <u>C4591009:</u> <u>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. 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.</u></li> </ul>
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**Table 38. Action Plan for Important Potential Risk “Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)”**

Milestones for evaluation and reporting	<ul style="list-style-type: none"> <li>• C4591001 (ongoing Study): <ul style="list-style-type: none"> <li>• <del>Protocol submission: 22 April 2020 (Initial version); 30 October 2020 (Amendment No. 9)</del></li> <li>• <del>CSR submission on completion of the first efficacy IA with 94 cases: 12 November 2020;</del></li> <li>• <del>CSR submission on completion of full efficacy analysis with 164 cases: November 2020;</del></li> <li>• CSR submission upon regulatory request: at any time.</li> <li>• CSR submission 6 months post Dose 2: 31 <del>December</del> <u>May</u> 2021;</li> <li>• Final CSR submission with supplemental follow-up: 31 August 2023.</li> </ul> </li> <li>• Three <u>observational</u> post-authorization <del>epidemiological</del> safety studies for EUA (C4591008, C4591011, and C4591012): <ul style="list-style-type: none"> <li>• <del>Protocols draft submission: November 2020</del></li> <li>• Interim study reports* will be <del>generated</del> <u>submitted on the following dates based on data collected within the following study periods</u> post-EUA <del>vaccination</del> in target populations: <ul style="list-style-type: none"> <li>• <del>31 March 2021</del></li> <li>– 30 June 2021</li> <li>– 31 December 2021</li> <li>– 30 June 2022</li> <li>– 31 December 2022</li> </ul> </li> <li>• <del>Reports will be submitted within 1 month of end of interim study period.</del></li> <li>• <del>Final study reports will be based on a study period of 30 months and submitted within 6 months of end of study.</del></li> <li>• <del>* Note: planned report dates assume vaccine availability on 01 December 2020</del> <u>submitted by 31 December 2023.</u></li> </ul> </li> <li>• C4591009: <ul style="list-style-type: none"> <li>• <u>Protocol submission: 31 August 2021</u></li> <li>• <u>Monitoring report submission: 31 October 2022</u></li> <li>• <u>Interim Analysis submission: 31 October 2023</u></li> <li>• <u>Final study report submission: 31 October 2025.</u></li> </ul> </li> </ul>
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## Action Plan for Missing Information

**Table 39. Action Plan for Missing Information “Use in Pregnancy and Lactation”**

Actions proposed	<ul style="list-style-type: none"> <li>• <u>C4591015: A phase 2/3, placebo-controlled, randomized, observer blind study to assess the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women who receive 18 years of age and older.</u></li> <li>• <u>C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States.</u></li> <li>• <u>C4591011: Active safety surveillance epidemiological studies designed to monitor pregnancies exposed to the Pfizer-BioNTech COVID-19 vaccine under EUA within the US. As feasible, for such individuals identified, data characterizing use, timing of exposure, and adverse pregnancy outcomes will be described. Department of Defense population following Emergency Use Authorization.</u></li> </ul>
Objective of proposed actions	<ul style="list-style-type: none"> <li>• <u>Clinical study: to C4591015: To assess safety and immunogenicity of Pfizer-BioNTech COVID-19 vaccine in pregnant women.</u></li> <li>• <u>Within</u> <u>In addition, exploratory objectives include:</u> <u>To describe the proposed real-world active surveillance studies, monitor for immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic Pfizer-BioNTech COVID-19 vaccination vaccine during pregnancy occurring under an EUA within.</u> <u>To describe the US, and characterize use and outcomes as feasible, safety of maternal immunization in infants born to breastfeeding maternal participants vaccinated with prophylactic Pfizer-BioNTech COVID-19 vaccine during pregnancy.</u></li> <li>• <u>C4591009<sup>a</sup>: To assess whether pregnant women experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine.</u></li> <li>• <u>C4591011<sup>a</sup>: 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 Pfizer-BioNTech COVID-19 vaccine.</u></li> </ul>
Rationale for proposed actions	Acquisition of data in an unstudied population with potentially different safety considerations from the time vaccine is available.

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**Table 39. Action Plan for Missing Information “Use in Pregnancy and Lactation”**

Monitoring by the sponsor for safety issue and proposed actions	<ul style="list-style-type: none"> <li>• <u>C4591015</u>: Monitoring via planned clinical study.</li> <li>• <u>C4591009</u>: <del>The proposed real-world active surveillance studies are designed collection of safety data in vaccine recipients, including pregnant women, is critical to monitor vaccination during pregnancy within populations expected to receive our understanding of the vaccine safety profile and to enable robust safety signal detection and evaluation and, if needed, further risk mitigation under BLA.</del></li> <li>• <u>C4591011</u>: <ol style="list-style-type: none"> <li>1. <u>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 Pfizer-BioNTech COVID-19 vaccine under EUA. As feasible, this are also planned.</u></li> <li>2. <u>Active surveillance strategy may be extended to obtain more comprehensive information to characterize use and outcomes of large numbers of individuals vaccinated with increasing real-world vaccination during pregnancy. 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 plans to conduct 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 their family members, as described in C4591011 (protocol submitted to FDA on 29 January 2021). The study period will be approximately 30 months following a availability of vaccine under EUA. The study will capture hospitalizations, deaths and serious safety events of interest, including anaphylaxis.</u></li> </ol> </li> </ul>
Milestones for evaluation and reporting	<ul style="list-style-type: none"> <li>• <u>C4591015</u>: <del>Protocol submission: February 2021</del> Primary endpoints completion: <u>30 April 2023.</u></li> <li>• <u>Protocols draft C4591009</u>: <ul style="list-style-type: none"> <li>• <u>Protocol submission: 31 August 2021</u></li> <li>• <u>Monitoring report submission: November 2020/31 October 2022</u></li> <li>• <u>Interim Analysis submission: 31 October 2023</u></li> <li>• <u>Final study report submission: 31 October 2025.</u></li> </ul> </li> <li>• <u>C4591011</u>: <ul style="list-style-type: none"> <li>• Interim study reports* will be <del>generated</del> <u>submitted on the following dates based on data collected within the following study periods post-EUA vaccination in target populations:</u> <ul style="list-style-type: none"> <li><del>31 March 2021</del></li> <li>– 30 June 2021</li> <li>– 31 December 2021</li> <li>– 30 June 2022</li> <li>– 31 December 2022</li> </ul> </li> <li>• <del>Reports will be submitted within 1 month of end of interim study period.</del></li> <li>• <del>Final study reports will be based on a study period of 30 months and submitted within 6 months of end of study.</del></li> <li>• <u>* Note: planned report dates assume vaccine availability on 01- will be submitted by 31 December 2023.</u></li> </ul> </li> </ul>

a. Study assesses pregnancy only.



**Table 40. Action Plan for Missing Information “Vaccine Effectiveness”**

Action proposed	<ul style="list-style-type: none"> <li>• <u><del>Non</del>C4591014: A non-interventional study (a test-negative design) study to evaluate the effectiveness of individuals presenting with symptoms of potential Pfizer-BioNTech COVID-19 vaccine against a cute respiratory illness due to SARS-CoV-2 infection among individuals &gt;16 years of age in a real-world setting. (Kaiser Permanente Southern California health system).</u></li> <li>• <u>WI235284: A low-interventional, test-negative design study to evaluate the effectiveness of Pfizer-BioNTech COVID-19 vaccine against a cute respiratory illness due to SARS-CoV-2 infection among individuals &gt;18 years of age in a real-world setting (Atlanta, Georgia, USA).</u></li> <li>• <u>WI255886: A low-interventional, test-negative design study to evaluate the effectiveness of Pfizer-BioNTech COVID-19 vaccine against a cute respiratory illness due to SARS-CoV-2 infection among individuals &gt;18 years of age in a real-world setting (Bristol, England, UK).</u></li> <li>• BNT162-01 cohort 13: Immunogenicity of Pfizer-BioNTech COVID-19 vaccine in immunocompromised subjects, including a assessment of antibody responses and cell-mediated responses.</li> </ul>
Objective of proposed actions	<ul style="list-style-type: none"> <li>• <u>C4591014: To estimate the effectiveness of <del>the recommended regimen</del> 2 doses of Pfizer-BioNTech COVID-19 vaccine against <del>potential COVID-19 illness requiring hospitalization and emergency department admission for a cute respiratory illness due to the ED or hospital where SARS-CoV-2 is identified infection.</del></u></li> <li>• <u>WI235284: To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 vaccine against hospitalization for a cute respiratory illness due to SARS-CoV-2 infection.</u></li> <li>• <u>WI255886: To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 vaccine against hospitalization for a cute respiratory illness due to SARS-CoV-2 infection.</u></li> <li>• <u>BNT-162-01 cohort 13: To assess potentially protective immune responses in immunocompromised adults.</u></li> </ul>
Rationale for proposed actions	<ul style="list-style-type: none"> <li>• <u>C4591014: To <del>assess real-world</del> determine the effectiveness <del>in comparison to</del> of Pfizer-BioNTech COVID-19 vaccine when administered outside of the clinical study efficacy results setting.</u></li> <li>• <u>WI235284: To determine the effectiveness of Pfizer-BioNTech COVID-19 vaccine when administered outside of the clinical setting.</u></li> <li>• <u>WI255886: To determine the effectiveness of Pfizer-BioNTech COVID-19 vaccine when administered outside of the clinical setting.</u></li> <li>• <u>BNT-162-01 cohort 13: To determine whether the Pfizer-BioNTech COVID-19 vaccine has potential to protect immunocompromised adults.</u></li> </ul>
Monitoring by the sponsor for safety issue and proposed actions	<ul style="list-style-type: none"> <li>• <u>C4591014: Use of primary and secondary data sources to monitor COVID-19 infection in vaccinated individuals.</u></li> <li>• <u>WI235284: Use of primary and secondary data sources to monitor COVID-19 infection in vaccinated individuals.</u></li> <li>• <u>WI255886: Use of primary and secondary data sources to monitor COVID-19 infection in vaccinated individuals.</u></li> <li>• <u>BNT-162-01 cohort 13: Reactogenicity, AE and SAE assessment.</u></li> </ul>

**Table 40. Action Plan for Missing Information “Vaccine Effectiveness”**

Milestones for evaluation and reporting	<ul style="list-style-type: none"> <li><u>Protocol submission: Q1 2021</u> <u>C4591014: Final CSR submission: 30 June 2023.</u></li> <li><u>Protocol WI235284: Final CSR submission: 30 June 2023.</u></li> <li><u>WI255886: Final CSR submission: November 2020</u> <u>30 June 2023.</u></li> <li><u>BNT-162-01 cohort 13: First IA submission: Q3 30 September 2021.</u></li> </ul>
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**Table 41. Action Plan for Missing Information “Use in Paediatric Individuals <16  
12 Years of Age”<sup>a</sup>**

Actions proposed	<ul style="list-style-type: none"> <li>C4591001: <math>\geq 12</math> to <math>\leq 15</math> 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. Randomised placebo-controlled study in 2000 subjects (1000 active vaccine) of 2 doses of <u>BNT162b2 Pfizer-BioNTech COVID-19 vaccine</u> at a 21-day interval.</li> <li><del>C4591007: <math>&lt; 12</math> 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, and efficacy study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children and adolescents <math>&gt; 5</math> to <math>&lt; 18</math> years of age.</del>  <del>Open uncontrolled escalating dose Phase 1 part, 16 subjects/dose level, up to 3 dose levels. Phase 2/3 part, randomized placebo-controlled study in 3000 subjects (1500 active vaccine) at selected dose level of BNT162b2 at a 21-day interval. Study C4591007 includes an option to study subjects 12 <math>&lt; 18</math> years of age if required, with a study design matching 5- to <math>&lt; 12</math> year old.</del></li> <li><u>Protocol number not yet assigned: 0 to <math>&lt; 5</math> years of age: A phase 1: open-label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, immunogenicity, and efficacy study of a SARS-CoV-2 RNA vaccine candidate against assessment of the 30-<math>\mu</math>g dose in 12- to 15-year-olds in the C4591001 study. The purpose of Phase 1 is to identify preferred dose level(s) of Pfizer-BioNTech COVID-19 in healthy toddlers, infants and children 0 to <math>&lt; 5</math> years of age.)</u> <u>Open uncontrolled escalating dose Phase 1 part, 16 subjects/dose level, vaccine from up to 3 different dose levels in each age group.</u> <u>Phase 2/3: Children <math>&gt; 5</math> to <math>&lt; 12</math> years of age, 12- are randomized 2:1 at selected dose level of Pfizer-BioNTech COVID-19 vaccine at a 21-day interval (2250 total subjects: 1500 active vaccine). Children 2 to <math>&lt; 5</math> years and 6 to 23 months of age, 7 to <math>&lt; 11</math> months of age and 0 to 6 months of age.</u> <u>Randomized 2:1 placebo-controlled study in 6400 subjects (3200 active vaccine) at selected dose levels of BNT162b2 level of Pfizer-BioNTech COVID-19 vaccine at a 21-day interval in 4 strata: 2 to <math>&lt; 5</math> years of (1125 total subjects per age group; 750 active vaccine per age, 12 to 23 months of age, 7 to <math>&lt; 11</math> months of age and 0 to 6 months of age, group).</u></li> <li><u>C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States.</u></li> </ul>
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**Table 41. Action Plan for Missing Information “Use in Paediatric Individuals <16  
12 Years of Age<sup>2</sup>”<sup>a</sup>**

Objective of proposed actions	<ul style="list-style-type: none"> <li>• C4591001: <del>≥12 to ≤15 years of age</del>: – Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response compared to subjects 16-25 years of age.</li> <li>• C4591007: <del>5 to &lt;12 years of age</del>: – Dose selection. Safety compared to placebo and immune-non-inferiority <del>of neutralizing antibody immune response compared to subjects 18-25 years of by 3 age</del>. Efficacy if sufficient cases accrue.</li> <li>• <del>0 to &lt;5 years of age</del>: – Dose selection. Safety compared to placebo and immune-non-inferiority cohorts of neutralizing antibody immune response compared to subjects 16-25 years of age. Efficacy if sufficient cases accrue.</li> <li>• <u>C4591009: To assess the occurrence of safety events of interest in a general US population (&lt;12 and ≥12 to ≤15 years of age) within selected data sources participating in the Sentinel System.</u></li> </ul>
Rationale for proposed actions	<ul style="list-style-type: none"> <li>• C4591001: <del>≥12 to ≤15 years of age</del>: Need to collect evidence of safety and effectiveness to support immunization in this age group.</li> <li>• C4591007: <del>5 to &lt;12 years of age</del>: Need to collect evidence of safety and effectiveness to support immunization in this age group.</li> <li>• <del>0 to &lt;5 years of age</del>: Need to collect evidence of safety and effectiveness to support immunization in this age group. <u>C4591009: Long-term surveillance of large numbers of individuals (&lt;12 and ≥12 to ≤15 years of age) 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.</u></li> </ul>

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**Table 41. Action Plan for Missing Information “Use in Paediatric Individuals <16  
12 Years of Age”<sup>22</sup>a**

Monitoring by the sponsor for safety issue and proposed actions	<ul style="list-style-type: none"> <li>• C4591001: <del>≥12 to ≤15 years of age:-</del> <ul style="list-style-type: none"> <li>• Electronic diary for reactogenicity 7 days following each dose of vaccine.</li> <li>• Adverse events for one month after second dose.</li> <li>• Serious Adverse Events for 6 months after the second dose.</li> <li>• Related SAEs and related deaths for 24 months after the second dose.</li> <li>• Collection of COVID-19 and MIS-C cases up to 24 months after the second dose.</li> </ul> </li> <li>• C4591007: <del>5 to</del> &lt;12 years of age:           <ul style="list-style-type: none"> <li>• Electronic diary for reactogenicity 7 days following each dose of vaccine.</li> <li>• Adverse events for one month after second dose.</li> <li>• Serious Adverse Events for 6 months after the second dose.</li> <li>• Related SAEs and related deaths for 24 months after the second dose.</li> <li>• Collection of COVID-19 and MIS-C cases up to 24 months after the second dose.</li> </ul> </li> <li>• <del>Protocol number not yet assigned: 0 to &lt;5</del> C4591009: &lt;12 and ≥12 to ≤15 years of age:           <ul style="list-style-type: none"> <li><del>• Electronic diary for reactogenicity 7 days following each dose of vaccine.</del></li> <li><del>• Adverse events for one month after second dose.</del></li> <li><del>• Serious Adverse Events for 6 months after the second dose.</del></li> <li><del>• Related SAEs and related deaths for 24 months after the second dose.</del></li> <li><del>• Collection of COVID-19 and MIS-C cases up to 24 months after the second dose.</del> <u>Longitudinal medical care information on outpatient medication dispensings, vaccine administrations, and inpatient and outpatient diagnoses and procedures in addition to adjudication of select events via medical records.</u></li> <li><u>Incidence rates and comparative incidence rate ratios of safety events of interest (AESIs from FDA’s BEST System<sup>90</sup> and CDC’s Vaccine Safety Data link<sup>91</sup> in addition to vaccine-associated enhanced respirator disease).</u></li> <li><u>Study period to start on date that Pfizer-BioNTech COVID-19 vaccine became available under EUA (December 11, 2020) and will end a minimum of 3 years after this date.</u></li> <li><u>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.</u></li> </ul> </li> </ul>
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**Table 41. Action Plan for Missing Information “Use in Paediatric Individuals <16 Years of Age”<sup>a</sup>**

Milestones for evaluation and reporting	<ul style="list-style-type: none"> <li>• C4591001: ≥12 to ≤15 years of age: <ul style="list-style-type: none"> <li>○ <del>Protocol (Amendment no. 7) submitted to BB IND 19736 on: 07 October 2020.</del></li> <li>• First report with up to 1-month post dose 2 (sa fety): <u>March 30 April 2021</u></li> <li>• Further reports: <ul style="list-style-type: none"> <li>– 6-month post dose 2 (sa fety): <u>31 July 2021</u></li> <li>– 24-month post dose 2 (sa fety): <u>31 January 2023.</u></li> </ul> </li> </ul> </li> <li>• C4591007: <del>5 to</del> &lt;12 years of age: <ul style="list-style-type: none"> <li>○ <del>Protocol submission: January 2021 (pending CBER feedback).</del></li> <li>• First report with up to <del>2 months</del> <u>1-month</u> post dose 2 <u>in ≥5 to &lt;12 years of age</u> (sa fety): <u>30 September 2021.</u></li> <li>• Further reports: <ul style="list-style-type: none"> <li>– 6-month post dose 2 (sa fety): <u>31 March 2022.</u></li> <li>– 24-month post dose 2 (sa fety): <u>30 September 2023.</u></li> </ul> </li> <li>• <del>Protocol number not yet assigned: 0 to &lt;5 years of age.</del></li> </ul> </li> <li>• <u>C4591009:</u> <ul style="list-style-type: none"> <li>• Protocol submission: <u>June 31 August 2021</u></li> <li>• <u>Study start planned by July 2021. Monitoring report submission: 31 October 2022</u></li> <li>• <u>Interim Analysis submission: 31 October 2023</u></li> <li>• <u>Final study report submission: 31 October 2025.</u></li> </ul> </li> </ul>
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a. Missing information has been re-worded to reflect current state

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### 3.1.4. Summary of Actions to be Completed, Including Milestones

**Table 42. Summary of Safety Concerns and Action Plans**

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
Anaphylaxis	<p><del>Ongoing C4591001</del>: 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.</p> <p><del>Ongoing (C4591001)</del></p>	To evaluate the safety, tolerability, immunogenicity, and efficacy of Pfizer-BioNTech COVID-19 vaccine. <del>Further, an</del> <u>An</u> 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.	<ul style="list-style-type: none"> <li>• CSR submission upon regulatory request:</li> <li>• CSR submission 6-month post Dose 2:</li> <li>• Final CSR submission with supplemental follow-up:</li> </ul>	<ul style="list-style-type: none"> <li>• At any time</li> <li>• 31 <del>December</del> <u>May</u> 2021</li> <li>• 31 August 2023</li> </ul>
	<p><u>C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States.</u></p> <p><u>Planned</u></p>	<u>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.</u>	<ul style="list-style-type: none"> <li>• <u>Protocol submission:</u></li> <li>• <u>Monitoring report submission:</u></li> <li>• <u>Interim analysis submission:</u></li> <li>• <u>Final study report submission:</u></li> </ul>	<ul style="list-style-type: none"> <li>• <u>31 August 2021</u></li> <li>• <u>31 October 2022</u></li> <li>• <u>31 October 2023</u></li> <li>• <u>31 October 2025</u></li> </ul>
	<p><u>Safety Surveillance C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 vaccine in the US Department of Defense Population population following emergency use authorization (C4591011). Emergency Use Authorization.</u></p> <p><u>Planned</u></p>	<u>Assessment of occurrence To assess whether individuals in the US DoD Military Health System (MHS) experience increased risk of safety events of interest, including severe or atypical following receipt of the Pfizer-BioNTech COVID-19 in a cohort of people within the Department of Defense Healthcare System vaccine.</u>	<ul style="list-style-type: none"> <li>• <u>Interim reports submission:</u></li> <li>• <u>Final study report submission:</u></li> </ul>	<ul style="list-style-type: none"> <li>• <u>31 March 2021</u></li> <li>• <u>30 June 2021</u></li> <li>• <u>31 December 2021</u></li> <li>• <u>30 June 2022</u></li> <li>• <u>31 December 2022</u></li> <li>• <u>31 December 2023</u></li> </ul>

**Table 42. Summary of Safety Concerns and Action Plans**

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
Anaphylaxis (Cont'd)	<u>C4591012</u> : Post-emergency use authorization active <u>safety surveillance of adverse events of special interest (AESI) study</u> among individuals in the Veteran's Affairs Health System receiving Pfizer-BioNTech COVID-19 vaccine ( <u>C4591012</u> ).  <u>Planned</u>	<u>Assessment of occurrence To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, including severe or atypical following receipt of the Pfizer-BioNTech COVID-19 in real-world use of COVID-19 mRNA vaccine.</u>	<ul style="list-style-type: none"> <li><u>Interim reports submission:</u></li> <li><u>Final study report submission:</u></li> </ul>	<u>31 March 2021</u> <ul style="list-style-type: none"> <li>30 June 2021</li> <li>31 December 2021</li> <li>30 June 2022</li> <li>31 December 2022</li> <li><u>31 December 2023</u></li> </ul>
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	<u>C4591001</u> : <del>Ongoing</del> 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 ( <u>C4591001</u> ).  <u>Ongoing</u>	<u>The objective of the study is to To</u> evaluate the safety, tolerability, immunogenicity, and efficacy of Pfizer-BioNTech COVID-19 vaccine.  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 <u>vaccine-associated enhanced disease, VAED/VAERD.</u> Surveillance is planned for 2 years following Dose 2	<ul style="list-style-type: none"> <li><u>Protocol CSR submission upon regulatory request:</u></li> <li><u>CSR submission 6-month post Dose 2:</u></li> <li><u>Final CSR submission with supplemental follow-up:</u></li> </ul>	<u>Any time 22 April 2020*</u> (Initial version) <ul style="list-style-type: none"> <li><u>30 October 2020</u> (Amendment No. 9)</li> <li><u>31 May 2021</u></li> <li><u>31 August 2023</u></li> </ul>
	<del>a.</del>		<del>CSR submission on completion of the first efficacy IA with 94 cases:</del>	<del>12 November 2020*</del>
			<del>CSR submission on completion of full efficacy analysis with 164 cases:</del>	<del>November 2020</del>
			<del>CSR submission upon regulatory request:</del>	<del>Any time</del>



**Table 42. Summary of Safety Concerns and Action Plans**

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
			<u>CSR submission 6 months post Dose 2:</u>	<u>December 2021</u>
			<u>Final CSR submission with supplemental follow up:</u>	<u>August 2023</u>
	<p><u>Three post-C4591008/C4591011/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</u></p> <p><u>C4591008: Ongoing</u> <u>C4591011/C4591012: Planned</u></p>	<p><u>Assessment of occurrence To characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease in real-world use of, among individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine since EUA</u></p>	<ul style="list-style-type: none"> <li><u>Protocol draft/Interim reports submission:</u></li> <li><u>Final study report submission:</u></li> </ul>	<ul style="list-style-type: none"> <li><u>November 2020-30 June 2021</u></li> <li><u>31 December 2021</u></li> <li><u>30 June 2022</u></li> <li><u>31 December 2022</u></li> <li><u>31 December 2023</u></li> </ul>
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) (Cont'd)	<p>C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States</p> <p><i>Planned</i></p>	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 Pfizer-BioNTech COVID-19 vaccine	<ul style="list-style-type: none"> <li><u>Interim reports/Protocol submission*:</u></li> <li><u>Monitoring report submission:</u></li> <li><u>Interim analysis submission:</u></li> <li><u>Final study report submission:</u></li> </ul>	<ul style="list-style-type: none"> <li><u>31 March/August 2021</u></li> <li><u>30 June 2021</u></li> <li><u>31 December 2021</u></li> <li><u>30 June/October 2022</u></li> <li><u>31 December 2022/October 2023</u></li> <li><u>31 October 2025</u></li> </ul>
			<u>Final CSR submission:</u>	<u>31 December 2023</u>
			<u>* Note: planned report dates assume vaccine availability on 01 December 2020</u>	



**Table 42. Summary of Safety Concerns and Action Plans**

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
Use in pregnancy and lactation	<u>C4591015: A phase 2/3, placebo-controlled, randomized, observer-blind, <del>planned clinical</del> study to assess/evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women who receive Pfizer-BioNTech COVID-19 vaccine, 18 years of age and older.</u>  <u>Ongoing</u>	<u>Safety To assess safety and immunogenicity of Pfizer-BioNTech COVID-19 vaccine in pregnant women.</u> <u>Exploratory objectives include:</u> <u>To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic Pfizer-BioNTech COVID-19 vaccine during pregnancy.</u> <u>To describe the safety of maternal immunization in infants born to breastfeeding maternal participants vaccinated with prophylactic Pfizer-BioNTech COVID-19 vaccine during pregnancy.</u>	<ul style="list-style-type: none"> <li><u>Primary endpoints completion: Protocol submission:</u></li> </ul>	<ul style="list-style-type: none"> <li><u>February 2021</u> <u>30 April 2023</u></li> </ul>
			<u>Primary endpoints completion:</u>	<u>April 2023</u>
Use in pregnancy and lactation (Cont'd)	<u>As feasible, monitor pregnancies exposed to the C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 vaccine, and as feasible, characterize use and outcomes in all of the planned post-authorization safety studies, the United States Department of Defense population following Emergency Use Authorization</u>  <u>Planned</u>	<u>Monitor pregnancies exposed to 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 Pfizer-BioNTech COVID-19 vaccine, and as feasible, characterize use and outcomes.</u>	<ul style="list-style-type: none"> <li><u>Protocol draft/Interim reports submission:</u></li> <li><u>Final study report submission:</u></li> </ul>	<ul style="list-style-type: none"> <li><u>November 2020</u> <u>30 June 2021</u> <u>31 December 2021</u> <u>30 June 2022</u> <u>31 December 2022</u></li> <li><u>31 December 2023</u></li> </ul>

**Table 42. Summary of Safety Concerns and Action Plans**

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
	C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States. <i>Planned</i>	To assess whether pregnant women, experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine.	<ul style="list-style-type: none"> <li>• <u>Interim reports Protocol submission:</u></li> <li>• <u>Monitoring report submission:</u></li> <li>• <u>Interim analysis submission:</u></li> <li>• <u>Final study report submission:</u></li> </ul>	<ul style="list-style-type: none"> <li>• 31 <del>March</del> <u>August</u> 2021</li> <li>• 30 <del>June</del> <u>2021</u></li> <li>• 31 <del>December</del> <u>2021</u></li> <li>• 30 <del>June</del> <u>October</u> 2022</li> <li>• 31 <del>December</del> <u>2022</u> <u>October 2023</u></li> <li>• 31 <del>October</del> <u>2025</u></li> </ul>
Vaccine effectiveness	C4591014: Non-interventional, test-negative design study to evaluate the effectiveness of Pfizer-BioNTech COVID-19 vaccine against a cute respiratory illness due to SARS-CoV-2 infection among individuals ≥16 years of age in a real-world setting (Kaiser Permanente Southern California health system). <i>Planned</i>	To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 vaccine against hospitalization and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.	<ul style="list-style-type: none"> <li>• Final CSR submission:</li> </ul>	<ul style="list-style-type: none"> <li>• 31 <del>December</del> <u>30 June</u> 2023</li> </ul>
			<i>Note: planned report dates assume vaccine availability on 01 December 2020</i>	

**Table 42. Summary of Safety Concerns and Action Plans**

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
Vaccine effectiveness <u>(Cont'd)</u>	<del>Non</del> <u>WI235284: A low-interventional study (a test-negative design) study to evaluate the effectiveness of individuals presenting with symptoms of potential Pfizer-BioNTech COVID-19 vaccine against a cute respiratory illness due to SARS-CoV-2 infection among individuals ≥18 years of age in a real-world setting (Atlanta, Georgia, USA).</u>  <u>Planned</u>	<del>Estimate</del> <u>To estimate the effectiveness of 2 doses/dosed of Pfizer-BioNTech COVID-19 vaccine against potential COVID-19 hospitalization for a cute respiratory illness requiring admission due to the ED or hospital where SARS-CoV-2 is identified infection.</u>	• <del>Protocol</del> <u>Final CSR</u> submission:	• <del>Q1 2021</del> <u>30 June 2023</u>
	WI255886: A low-interventional, test-negative design study to evaluate the effectiveness of Pfizer-BioNTech COVID-19 vaccine against a cute respiratory illness due to SARS-CoV-2 infection among individuals ≥18 years of age in a real-world setting (Bristol, England, UK).  <u>Planned</u>	To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 vaccine against hospitalization for a cute respiratory illness due to SARS-CoV-2 infection.	• Final CSR submission:	• <u>30 June 2023</u>
	BNT162-01 cohort 13: Immunogenicity of Pfizer-BioNTech COVID-19 vaccine in immunocompromised subjects, including a ssessment of antibody responses and cell-mediated responses.  <u>Ongoing</u>	To assess potentially protective immune responses in immunocompromised adults.	• <del>Protocol</del> <u>First IA</u> submission:	• <del>November 2020</del> <u>30 September 2021</u>
			<del>First IA submission:</del>	<del>Q3 2021</del>

**Table 42. Summary of Safety Concerns and Action Plans**

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
Use in <del>paediatric</del> pediatric individuals <del>&lt;16</del> 12 years of age	<u>C4591001</u> ≥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 ( <del>C4591001</del> ). <u>Ongoing</u>	Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response compared to subjects 16-25 years of age.	<ul style="list-style-type: none"> <li><u>Protocol (Amendment no. 7) submitted to BB IND 19736</u></li> <li><u>First report with up to 1-month post dose 2 (sa fety):</u></li> <li><u>Report 6-month post dose 2 (sa fety):</u></li> <li><u>Report 24-month post dose 2 (sa fety):</u></li> </ul>	<ul style="list-style-type: none"> <li><u>07 October 2020</u> <u>30 April 2021</u></li> <li><u>31 July 2021</u></li> <li><u>31 January 2023</u></li> </ul>
			<u>First report with up to 1-month post dose 2 (sa fety)</u>	<u>March 2021</u>
			<u>Report 6-month post dose 2 (sa fety)</u>	<u>July 2021</u>
			<u>Report 24-month post dose 2 (sa fety)</u>	<u>January 2023</u>
	<del>5 to</del> <u>C4591007</u> <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, <u>and</u> immunogenicity, <u>and</u> efficacy study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children <u>and</u> adolescents <u>≥ 5 to &lt;18</u> <12 years of age ( <del>C4591007</del> ). <u>Ongoing (started in March)</u>	Dose selection. Safety compared to placebo and immune-non-inferiority <u>by 3 age cohorts</u> of neutralizing antibody immune response compared to subjects <del>18</del> 16-25 years of age. Efficacy if sufficient cases accrue.	<ul style="list-style-type: none"> <li><u>Protocol submission</u></li> <li><u>First report with up to 1-month post dose 2 (sa fety) in &gt;5 to &lt;12 years of age:</u></li> <li><u>Report 6-month post dose 2 (sa fety) in &gt;5 to &lt;12 years of age:</u></li> <li><u>Report 24-month post dose 2 (sa fety) in &gt;5 to &lt;12 years of age:</u></li> </ul>	<ul style="list-style-type: none"> <li><u>January 30 September 2021</u> <del>(pending CBER feedback)</del></li> <li><u>31 March 2022</u></li> <li><u>30 September 2023</u></li> </ul>
	<u>2</u>		<u>First report with up to 2-months post dose 2 (sa fety):</u>	<u>September 2021</u>

**Table 42. Summary of Safety Concerns and Action Plans**

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
			<u>Report 6-month post dose 2 (safety):</u>	<u>March 2022</u>
			<u>Report 24-month post dose 2 (safety)</u>	<u>September 2023</u>
	<p><u>0 to &lt;5 years of age:</u>  <u>A phase 1 open label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, immunogenicity, and efficacy study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy toddlers, infants and children 0 to &lt;5 years of age (Protocol number not yet assigned). C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States.</u>  <u>Planned</u></p>	<p><u>Dose selection. Safety compared to placebo and immune non-inferiority of neutralizing antibody immune response compared to subjects 16-25 years of age. Efficacy if sufficient cases accrue. To assess the occurrence of safety events of interest in a general US population (&lt;12 and &gt;12 to &lt;15 years of age) within selected data sources participating in the Sentinel System.</u></p>	<ul style="list-style-type: none"> <li><u>Protocol submission;</u></li> <li><u>Monitoring report submission;</u></li> <li><u>Interim analysis submission;</u></li> <li><u>Final study report submission;</u></li> </ul>	<ul style="list-style-type: none"> <li><u>June 31 August 2021</u></li> <li><u>31 October 2022</u></li> <li><u>31 October 2023</u></li> <li><u>31 October 2025</u></li> </ul>
	<u>a.—</u>		<u>Study start planned by:</u>	<u>July 2021</u>

a.— Indicates the effective date of submission.

## ANNEX

### 3.2. Pharmacovigilance Methods

- BNT162b2 Vaccine: Pfizer-BioNTech COVID-19 Vaccine 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. Design and Conduct~~ List of Observational Studies

#### ~~3.2.2.3.2.1. EUA Safety Surveillance Study Included in the Pharmacovigilance Plan:~~ Attachment 1

- ~~Post authorization epidemiological safety studies: Attachment 2, Attachment 3, Attachment 4.~~

C4591001

C4591007

C4591008

C4591009

C4591011

C4591012

C4591014

C4591015

BNT162-01 cohort 13

WI235284

WI255886

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