COVID-19 mRNA VACCINE

RISK MANAGEMENT PLAN (RMP)

For a summary of the RMP, please refer to PART VI.

COMIRNATY (COVID-19 mRNA VACCINE)

RISK MANAGEMENT PLAN

RMP Version number: 2.0

Data lock point for this RMP: See below

12-15 years of age	13 March 2021 (Pfizer Clinical Database)
	28 February 2021 (Pfizer Safety Database)
16 years and older	14 November 2020 (Pfizer Clinical Database)
	02 October 2020 (BioNTech Clinical Database)
	17 December 2020 (Pfizer Safety Database for Anaphylaxis safety concern)

Date of final sign off: 29 April 2021

Rationale for submitting an updated RMP: This Type II variation includes an updated Comirnaty EU-RMP, focusing data on paediatric individuals 12 and 15 years of age. Upon CHMP positive opinion received on 15 April 2021 for the type II variation EMEA/H/C/005735/II/0019, the 3 vaccine effectiveness studies (C4591014, WI235284 and WI255886) were added in Part A of Annex 3.

Summary of significant changes in this RMP:

RMP Part/Module	Major Change (s)
PART I. PRODUCT(S) OVERVIEW	Proposed indication updated to include individuals aged 12-15 years.
PART II. SAFETY SPECIFICATION	
Module SI. Epidemiology of the Indication(s) and Target Populations	Epidemiology data updated with the most recent data available including data on individuals aged 12-15 years.
Module SII. Non-Clinical Part of the Safety Specification	Editorials.
Module SIII. Clinical Trial Exposure	Exposure data for participants 12-15 years of age added.
Module SIV. Populations Not Studied in Clinical Trials	Text updated with data for participants 12-15 years of age.
Module SV. Post-Authorisation Experience	Post authorisation exposure data added.
Module SVI. Additional EU Requirements for the Safety Specification	Editorials.
Module SVII. Identified and Potential Risks	Data from the clinical trial database and safety database for participants 12-15 years of age added only for the Important Identified and Potential Risks.

RMP Part/Module	Major Change (s)
Module SVIII. Summary of the Safety Concerns	No changes made.
PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	Editorials.
PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES	No changes made.
PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	No changes made.
PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	Indication updated to include individuals aged 12-15 years.
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 3: - C4591014, WI235284 and WI255886 added in Part A. Annex 8: - Changes respect version 1.1 added.

Other RMP versions under evaluation:

None

Details of the currently approved RMP

Version number: 1.1

Approved with procedure: EMEA/H/C/005735/II/0019

Date of approval (opinion date): 15 April 2021

QPPV name[1]: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

Abbreviation	Definition of Term
AE	adverse event
AESI	Adverse event of special interest
A:G	albumin:globulin
ARDS	acute respiratory distress syndrome
BALB/c	bagg albino
BC	Brighton Collaboration
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
ECDC	European Center for Disease Control
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EHR	electronic health records
EMA	European Medicines Agency
EUA	emergency use authorisation
EU	European Union
FDA	(US) Food and Drug Administration
GLP	good laboratory practice
HbA1c	glycated haemoglobin
HBV	hepatitis b virus
HCV	hepatitis c virus
HIV	human immunodeficiency virus
IA	interim analysis
ICU	intensive care unit
IFN	interferon
IL-4	interleukin-4
IM	intramuscular(ly)
IMD	index of multiple deprivation
IND	investigational new drug
LNP	lipid nanoparticle
MAA	marketing authorisation applicant
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition of Term
MERS-CoV	middle east respiratory syndrome–coronavirus
MIS-C	multisystem inflammatory syndrome in children
mRNA	messenger ribonucleic acid
NDA	new drug application
NHP	nonhuman primate
NICE	National Institute for Health and Care Excellence
OCS	oral corticosteroids
PC	product complaint
PK	pharmacokinetic
PVP	pharmacovigilance plan
RA	rheumatoid arthritis
RBC	red blood cell
RMP	risk management plan
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
siRNA	small-interfering RNA
SMQ	standardised MedDRA query
SmPC	summary of product characteristics
SPEAC	Safety Platform for Emergency vACcines
TESSy	The European Surveillance System
Th1	T helper cell type 1
Th2	T helper cell type 2
TME	targeted medical event
UK	United Kingdom
US	United States
V8	variant 8
V9	variant 9
VAC4EU	Vaccine monitoring Collaboration for Europe
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
WBC	white blood cells
WHO	World Health Organisation
WOCBP	women of child-bearing potential

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	COVID-19 mRNA Vaccine is single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorisation Applicant	BioNTech Manufacturing GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Comirnaty
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class Nucleoside-modified messenger RNA is formulated in LNP
	Summary of mode of action The nucleoside-modified messenger RNA in Comirnaty is formulated in LNPs, which enable delivery of the non replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.
	Important information about its composition The COVID-19 mRNA Vaccine: – is nucleoside-modified messenger RNA formulated in LNPs; – is a white to off-white frozen dispersion (pH:6.9 – 7.9). – Excipients: • ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315) • 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159) • 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC) • cholesterol, • potassium chloride, • potassium dihydrogen phosphate, • sodium chloride, • disodium phosphate dihydrate, • sucrose, • water for injections.
Hyperlink to the Product Information:	Please refer to Module 1.3.1 of this submission
Indication in the EEA	Proposed: Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older.

Dosage in the EEA	Proposed: Administered intramuscularly after dilution as a course of 2 doses (0.3 mL each) at least 21 days apart.
Pharmaceutical form and strengths	Proposed: Concentrate dispersion for injection. After dilution each vial contains 6 doses of 0.3 mL
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indication

Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older**.**

Incidence:

The COVID-19 is caused by a novel coronavirus labelled as SARS-CoV-2. The disease first emerged in December 2019, when a cluster of patients with pneumonia of unknown cause was recognised in Wuhan City, Hubei Province, China.[1] 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.[2]

Estimates of SARS-CoV-2 incidence change rapidly. The MAH obtained incidence and prevalence estimates using data from Worldometer, a trusted independent organisation that collects COVID-19 data from official reports and publishes current global and country-specific statistics online.[3]

As of 03 March 2021, the overall number of people who had been infected with SARS--CoV--2 was over 115 million worldwide,[4] an increase of nearly 100 million in the 7 months since 28 July 2020.[5] Table 1 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.[4]

In the US, the number of confirmed cases had reached over 29 million cases (8,864 per 100,000 people) by 03 March 2021.[4] This is an increase from 4.5 million (1,357 per 100,000) by 28 July 2020.[6]

Table 1. Incidence, Prevalence, and Mortality of COVID-19 as of 03 March 2021[4]

	Total Cases	Incidence: Total Cases/ 100,000	Active Cases[a]	Prevalence: Active Cases/ 100,000	Total Deaths	Mortality: Deaths / 100,000	Population
Global	115,760,943	1,485	21,707,680	278	2,571,518	33	7,794,824,793
EU-27	22,642,536	5,083	6,113,464	1,462	553,363	124	445,424,167
UK	4,194,785	6,157	1,065,282	1,564	123,783	182	68,125,249
EU-27 + UK	26,837,321	5,226	7,178,746	1,398	677,146	132	513,549,416
US	29,456,377	8,864	8,921,400	2,685	531,652	160	332,304,437

Table 1. Incidence, Prevalence, and Mortality of COVID-19 as of 03 March 2021[4]

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

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

The reported numbers refer only to cases that have been tested and confirmed to be carrying the virus. There are large geographic variations in the proportion of the population tested as well as in the quality of reporting across countries. People who carry the virus but remain asymptomatic are less likely to be tested and therefore mild cases are likely underreported. The numbers should therefore be interpreted with caution.[5]

Prevalence:

The prevalence of SARS-CoV-2 infection is defined as active cases per 100,000 people including confirmed cases in people who have not recovered or died. On 03 March 2021, the overall prevalence for the EU and UK (though not available for Sweden and the Netherlands) was 1,398 active cases per 100,000,[4] compared to 51 per 100,000 on 28 July 2020.[5] The range of reported prevalence was 81 to 6,019 per 100,000: Croatia, Denmark, and Germany reported the lowest prevalence while Belgium, France and Ireland reported the highest (Table 1).

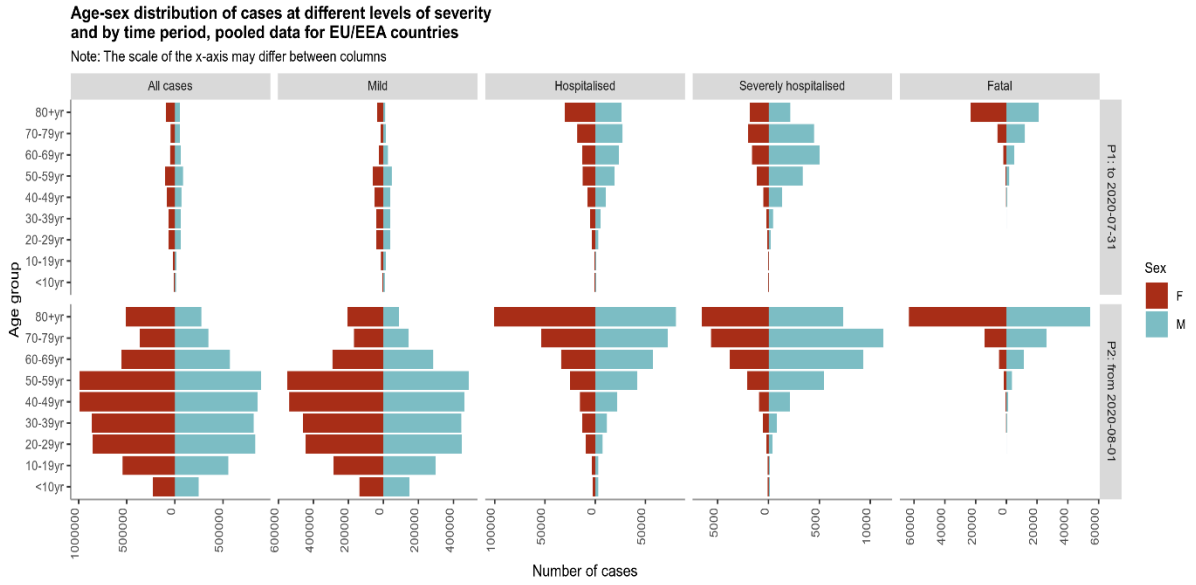
In the US, the prevalence on 03 March 2021 was nearly twice as high as the combined EU+UK estimates, with 2,685 active cases per 100,000.[4] The prevalence in the US was 653 per 100,000 on 28 July 2020.[5]

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

Since the beginning of the pandemic, the ECDC has continuously collected COVID-19 information from all countries who are members of EU/EEA and the UK. In the ECDC's TESSy database, COVID-19 case-based data, including age and gender, are available for over 80% of the official number of cases reported by ECDC epidemic intelligence,[7] 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.[8]

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

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



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

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

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 2.[9] 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 2. 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[9,a]

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

Table 2. 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[9,a]

								Age x Sex %	
Event	**Age Group**	**Age %**	**Sex**	**Sex %**	**Race[b]**	**Race %**	**Age Group**	**Males**	**Females**
Deaths	**0-4**	<0.1	**Males**	54.3	**H/L**	12.2	**0-4**	47.6	52.4
	5-17	0.1	**Females**	45.7	**AI/AN**	1	**5-17**	57.7	42.3
	18-29	0.5			**Asian**	4.3	**18-29**	63	37
	30-39	1.1			**Black**	14.7	**30-39**	66	34
	40-49	2.8			**NH/PI**	0.2	**40-49**	66.5	33.5
	50-64	14.5			**White**	63.1	**50-64**	65	35
	65-74	21.3			**M/O**	4.4	**65-74**	61.4	38.6
	75-84	27.7					**75-84**	55.8	44.2
	85+	32.1					**85+**	41.8	58.2

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

In general, disease has been much less severe among ages 0-24 compared to ages ≥25 years, with 2.5% hospitalised, 0.8% admitted to an intensive care unit, and <0.1% dying among ages 0-24, versus 16.6% hospitalised, 8.6% intensive care, and 5% dying among ages ≥25 years.[10] Among hospitalised 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.[11] The majority (approximately 60%) of COVID-19 patients admitted to hospitals in the US have been male.[11,12,13,14,15]

African American COVID-19 patients have been reported to have an increased risk of hospitalisation[12,16] and mortality,[17] 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.[18] 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.[19] 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.[20] 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, 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.[21] 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.[21,22,23] 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 3).[24] Risk of infection is also higher among some ethnic minority groups.[25,26]

Table 3. Risk for COVID-19 Infection, Hospitalisation, and Death by Age Group [24] and by Race/Ethnicity [25]

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

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

Risk for severe or fatal COVID-19 disease has been shown to increase with older age, male sex, or ethnic minority status.[24,25,26,27,28,29] Risks of hospitalisation and death increase dramatically for every 10-year age group above age 17 (Table 3).[24,29] Table 3 also gives estimated rate ratios for COVID-19 hospitalisation and death by race/ethnicity relative to white, non-Hispanic persons in the US. The highest risks of hospitalisation and death were observed among American Indian or Alaska native persons (RR = 3.7 for hospitalisation and 2.4 for death) and Hispanic or Latino persons (RR = 3.2 for hospitalisation 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.[25]

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 neighbourhoods with higher rates of limited English proficiency.[26,28,29,30] The CDC has also

recognised 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/behavioural disorders; people living in rural communities, nursing homes, long-term care facilities, or prisons; people experiencing homelessness; and newly resettled refugee populations.[31]

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.[26,27,28,29,30] Table 4 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.[29]

Table 4. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death[29]

		COVID-19 death Hazard Ratio	
Characteristic	**Category**	**Adjusted for age and sex**	**Fully adjusted**
Age	18-39	0.05 (0.04-0.07)	0.06 (0.04-0.08)
	40-49	0.28 (0.23-0.33)	0.30 (0.25 - 0.36)
	50-59	1.00 (ref)	1.00 (ref)
	60-69	2.79 (2.52-3.10)	2.40 (2.16-2.66)
	70-79	8.62 (7.84-9.46)	6.07 (5.51-6.69)
	80+	38.29 (35.02-41.87)	20.60 (18.70-22.68)
Sex	Female	1.00 (ref)	1.00 (ref)
	Male	1.78 (1.71-1.85)	1.59 (1.53-1.65)
BMI (kg/m^2)	Not obese	1.00 (ref)	1.00 (ref)
	30-34.9 (obese class I)	1.23 (1.17–1.30)	1.05 (1.00–1.11)
	35-39.9 (obese class II)	1.81 (1.68–1.95)	1.40 (1.30–1.52)
	40+ (obese class III)	2.66 (2.39–2.95)	1.92 (1.72–2.13)
Smoking	Never	1.00 (ref)	1.00 (ref)
	Former	1.43 (1.37–1.49)	1.19 (1.14–1.24)
	Current	1.14 (1.05–1.23)	0.89 (0.82–0.97)
Ethnicity[a]	White	1.00 (ref)	1.00 (ref)
	Mixed	1.62 (1.26–2.08)	1.43 (1.11–1.84)
	South Asian	1.69 (1.54–1.84)	1.45 (1.32–1.58)
	Black	1.88 (1.65–2.14)	1.48 (1.29–1.69)
	Other	1.37 (1.13–1.65)	1.33 (1.10–1.61)
IMD quintile[e]	1 (least deprived)	1.00 (ref)	1.00 (ref)
	2	1.16 (1.08-1.23)	1.12 (1.05–1.19)
	3	1.31 (1.23–1.40)	1.22 (1.15–1.30)
	4	1.69 (1.59–1.79)	1.51 (1.42–1.61)
	5 (most deprived)	2.11 (1.98–2.25)	1.79 (1.68–1.91)
Blood pressure	Normal	1.00 (ref)	1.00 (ref)
	High BP or diagnosed hypertension	1.09 (1.05–1.14)	0.89 (0.85–0.93)
Respiratory disease excluding asthma		1.95 (1.86–2.04)	1.63 (1.55–1.71)

Table 4. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death[29]

		COVID-19 death Hazard Ratio	
Characteristic	**Category**	**Adjusted for age and sex**	**Fully adjusted**
Asthma[b] (vs. none)	With no recent OCS use	1.13 (1.07–1.20)	0.99 (0.93–1.05)
	With recent OCS use	1.55 (1.39–1.73)	1.13 (1.01–1.26)
Chronic heart disease		1.57 (1.51–1.64)	1.17 (1.12–1.22)
Diabetes[c] (vs. none)	With HbA1c < 58 mmol/mol	1.58 (1.51–1.66)	1.31 (1.24–1.37)
	With HbA1c ≥ 58 mmol/mol	2.61 (2.46–2.77)	1.95 (1.83–2.08)
	With no recent HbA1c measure	2.27 (2.06–2.50)	1.90 (1.72–2.09)
Cancer (non-hematological, vs. none)	Diagnosed <1 year ago	1.81 (1.58–2.07)	1.72 (1.50–1.96)
	Diagnosed 1-4.9 years ago	1.20 (1.10–1.32)	1.15 (1.05–1.27)
	Diagnosed ≥ 5 years ago	0.99 (0.93–1.06)	0.96 (0.91–1.03)
Hematological malignancy (vs. none)	Diagnosed <1 year ago	3.02 (2.24–4.08)	2.80 (2.08–3.78)
	Diagnosed 1-4.9 years ago	2.56 (2.14–3.06)	2.46 (2.06–2.95)
	Diagnosed ≥ 5 years ago	1.70 (1.46–1.98)	1.61 (1.39–1.87)
Reduced kidney function[d] (vs. none)	eGFR 30-60	1.56 (1.49–1.63)	1.33 (1.28–1.40)
	eGFR < 30	3.48 (3.23–3.75)	2.52 (2.33–2.72)
Liver disease		2.39 (2.06–2.77)	1.75 (1.51–2.03)
Stroke or dementia		2.57 (2.46–2.70)	2.16 (2.06–2.27)
Other neurological disease		3.08 (2.85–3.33)	2.58 (2.38–2.79)
Organ transplant		6.00 (4.73–7.61)	3.53 (2.77–4.49)
Asplenia		1.62 (1.19–2.21)	1.34 (0.98–1.83)
Rheumatoid arthritis, lupus, or psoriasis		1.30 (1.21–1.38)	1.19 (1.11–1.27)
Other immunosuppressive condition		2.75 (2.10–3.62)	2.21 (1.68–2.90)

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

The main existing treatment options:

Through 28 February 2021, other COVID-19 vaccines were authorised in the European Union including vaccines from Moderna (EU/1/20/1507) and AstraZeneca (EU/1/21/1529). Others may subsequently be approved.

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

Symptoms of COVID-19

The clinical manifestations of COVID-19 vary widely, from asymptomatic infection in 17-20%,[32,33] to critical illness and death. The most common symptoms of COVID-19 are fever, cough, and shortness of breath (Table 5).[34]

Table 5. Signs and Symptoms among 291 Paediatric (age <18 years) and 10,944 Adult (age 18–64 years) Patients[a] with Laboratory confirmed COVID-19 — United States, February 12–April 2, 2020[34]

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

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

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.[35,36] 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 hospitalised if conditions worsen.[36] 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.[35]

Progression and Timeline of Severe Disease Requiring Hospitalisation

Those with severe disease will require hospitalisation 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.[37] For the week ending 28 February 2021, 10 patients per 100,000 population were hospitalised due to COVID-19 in 22 countries of the EU/EEA with available data.[38]

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%).[39,40,41,42] Approximately 17% to 40% of those hospitalised with COVID-19

experience severe symptoms necessitating intensive care.[11,16,39] More than 75% of patients hospitalised with COVID-19 require supplemental oxygen.[43]

Studies early in the pandemic demonstrated that time from onset of illness to ARDS was 8-12 days and time from onset of illness to ICU admission was 9.5–12 days.[35] In 17 countries of the EU/EEA with available data, 1.8 patients per 100,000 population were in the ICU due to COVID-19 for the week ending 28 February 2021.[38] A recent meta-analysis found that, of patients <19 years of age, 11% went to the ICU, non-invasive ventilation was administered among 12%, and 4% required mechanical ventilation.[33]

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).[37] 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).[44] 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).[45] According to a recent meta-analysis of paediatric studies published through October 2020, the mortality for patients <19 years of age is 2%.[33]

Mortality data are also presented from Worldometer, an independent organisation that publishes current, reliable COVID-19 statistics online.[6] The mortality of SARS-CoV-2 infection is defined as the cumulative number of deaths among detected cases.

As of 03 March 2021, the overall SARS-CoV-2 mortality for the EU + UK was 677,146 deaths, or 132 per 100,000 people. Reported mortality among EU countries and the UK ranged from 14 to 195 deaths per 100,000 (Table 1). Finland and Cyprus reported the lowest mortality; Czech Republic, Belgium and Slovenia reported the highest.[4]

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. [4]

Overall reported mortality among hospitalised COVID-19 patients varies from 12.8% to 26% in the EU and UK. [16,18,46,47] Mortality rates are declining over time, presumably due to an improved understanding of COVID-19 and its management.[46,48]

Complications of COVID-19 and Long-COVID

Complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney, and coagulation system.[11,13,42] 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.[49]

COVID-19 symptoms can persist weeks or months beyond the acute infection.[50,51] 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).[52]

A meta-analysis of 31 studies among patients between 18 to 49 years of age found that COVID-19 symptoms were experienced for 14 days to 3 months post-infection, including persistent fatigue (39–73%), breathlessness (39–74%), decrease in quality of life (44–69%), impaired pulmonary function, abnormal CT findings including pulmonary fibrosis (39–83%), evidence of peri-/perimyo-/myocarditis (3–26%), changes in microstructural and functional brain integrity with persistent neurological symptoms (55%), increased incidence of psychiatric diagnoses (5.8% versus 2.5–3.4% in controls), and incomplete recovery of olfactory and gustatory dysfunction (33–36%).[53] 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.[54,55,33]

Important co-morbidities:

Important comorbidities in hospitalised COVID-19 patients include hypertension, diabetes, obesity, cardiovascular disease, chronic pulmonary disease or asthma, chronic kidney disease, cancer, and chronic liver disease.[12,13,14,39,42] Prevalence of these conditions have been reported to be lower in mild cases and higher among fatal cases, as shown for European countries in Table 6 below.

Table 6. Preconditions among COVID-19 Patients in EU/EEA and UK, by Severity of Disease. Case-based Data from TESSy Produced 04 March 2021

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

Abbreviation: Hosp = Hospitalised

Table 7 below summarises 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.[26] The most common comorbidities were similar in the full cohort and among those who tested positive: obesity, hypertension, diabetes, and asthma. Among those hospitalised 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 7. 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[26]

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

Module SII. Non-Clinical Part of the Safety Specification

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

Nonclinical studies in mice and NHP for BNT162b2 (COVID-19 mRNA vaccine) demonstrated both a strong neutralizing antibody response and a Th1-type $CD4^+$ and an $IFN\gamma^+$ $CD8^+$ T-cell response. The Th1 profile is characterised by a strong IFNγ, but not IL-4, response indicating the absence of a potentially deleterious Th2 immune response and is a pattern favored for vaccine safety and efficacy.[56] Rhesus macaques (Study VR-VRT-10671) that had received two IM immunisations with 100 µg BNT162b2 or saline 21 days apart were challenged with 1.05×10^6 plaque forming units of SARS-CoV-2 (strain USA-WA1/2020), split equally between the intranasal and intratracheal routes.[57] BNT162b2 provided complete protection from the presence of detectable viral RNA in the lungs compared to the saline control with no clinical, radiological or histopathological evidence of vaccine-elicited disease enhancement.

An intravenous rat PK study, using an LNP with the identical lipid composition as COVID-19 mRNA 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 COVID-19 mRNA 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 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 metabolised 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 COVID-19 mRNA vaccine candidate were tested, designated “variant 8” and “variant 9” (V8 and V9, respectively). The variants differ only in their codon optimisation sequences which are designed to improve antigen expression, otherwise the amino acid sequences of the encoded antigens are identical.

COVID-19 mRNA 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. A DART study in Wistar Han rats has been completed. Safety pharmacology, genotoxicity and carcinogenicity studies have not been conducted, in accordance with the 2005 WHO vaccine guideline.[58]

The IM route of exposure was selected for nonclinical investigation 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 COVID-19 mRNA 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 oedema and erythema at the injection sites, transient elevation in body temperature, elevations in WBC count and acute phase reactants, and lower A:G ratios. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunisations. Changes secondary to inflammation included slight and transient reduction in body weights and transient reduction in reticulocytes, platelets and RBC mass parameters. Decreased reticulocytes were reported in rats treated with the licensed LNP-siRNA pharmaceutical Onpattro™ (NDA # 210922) but have not been observed in humans treated with this biotherapeutic[59] 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 haemostasis. Elevated levels of gamma-glutamyl transferase were observed in the first repeat-dose toxicity study with COVID-19 mRNA vaccine (V8) without evidence of cholestasis or hepatobiliary injury but was not recapitulated in the second repeat dose-toxicity study with COVID-19 mRNA 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 COVID-19 mRNA 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 COVID-19 mRNA 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 oedema 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 portal hepatocytes, the only test article-related liver microscopic finding, was not associated with any microscopic evidence of hepatic injury or hepatic functional effects (i.e., liver functional enzymes were not elevated) and may be associated with hepatocyte uptake of the LNP lipids.[60] 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 COVID-19 mRNA vaccine. A robust immune response was elicited to the COVID-19 mRNA vaccine antigen.

In summary, the nonclinical safety findings related to COVID-19 mRNA 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 COVID-19 mRNA vaccine from nonclinical studies and their relevance to human usage are presented in Table 8. There was no evidence of vaccine-elicited disease enhancement.

Table 8. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Nonclinical Studies[a,b]	Relevance to Human Usage
Pharmacology	
NHP Challenge Model • No evidence of vaccine-elicited disease enhancement.	• Suggests low risk of vaccine-enhanced disease in humans; being investigated in CTs.
Toxicity	
Injection site reactions: • Injection site reactions were common and reversible or showed signs of reversibility at the end of the 3-week recovery period in nonclinical studies.	• In common with other vaccines, COVID-19 mRNA vaccine administration has the potential to generate injection site reactions such as oedema and erythema at the injection sites.
Inflammation and immune activation: • Evidence of inflammation or immune activation was common, reversible, and included transiently higher body temperature, higher circulating WBCs, and higher acute phase reactants. Secondarily, transiently lower body weights, reticulocytes, platelets, and RBC mass parameters were observed.	• In common with all vaccines, COVID-19 mRNA vaccine administration has the potential to generate inflammation which can lead to increased body temperature, higher circulating WBCs and higher acute phase proteins. • Decreased reticulocytes have not been observed in humans treated with the LNP-siRNA pharmaceutical Onpattro[59], suggesting this finding in rats is a species-specific effect. • COVID-19 mRNA 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.
Developmental and Reproductive Toxicity[b] • No vaccine-related effects on female fertility or the development of fetuses or offspring were observed in a DART study of BNT162b2 in rats.	• No effects are anticipated in WOCBP, pregnant women or their offspring.

a. Safety pharmacology, genotoxicity, and carcinogenicity studies were not conducted, in accordance with 2005 WHO vaccine guideline, as they are generally not considered necessary to support development and licensure of vaccines for infectious diseases.[58] In addition, the components of the vaccine construct are lipids and RNA and are not expected to have carcinogenic or genotoxic potential.
b. Based on audited study data. A DART study evaluating COVID-19 mRNA vaccine will be completed by 31 Mar 2021.

Module SIII. Clinical Trial Exposure

BioNTech is conducting a first-in-human dose level–finding Phase 1/2 study (BNT162-01) in Germany to gather safety and immunogenicity data to enable evaluation of 4 vaccines candidates individually to inform the overall clinical development of a COVID-19 mRNA vaccine.

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

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

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. COVID-19 mRNA 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 COVID-19 mRNA vaccine was more favourable than BNT162b1 in both younger and older adults with similar immunogenicity results;
- in the NHP challenge study (VR-VTR-10671 – see Module SII), a trend toward earlier clearance of COVID-19 mRNA vaccine was observed in the nose.

Phase 2 of the study (for which enrolment 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 enrolment of participants 16 to 17 years of age to be evaluated with the 18- to 55-year-old cohort, as well as enrolment of a 12- to 15-year-old cohort, and immunogenicity data from participants 12- to 15-year-old cohort (Table 20 through Table 24) are anticipated to bridge to the 16- to 25-year-old cohort.

The pivotal study was initially planned to enrol 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 enrol 46,333 participants, which slightly enhanced the ability to detect AEs. However, rarer events might not be detected.

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

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

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

Ongoing COVID-19 mRNA 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 randomised 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 randomised participants in 5 study arms.

Population for analysis of CTs data in this RMP includes the following 2 studies:

- C4591001: *Phase 1/2/3, placebo-controlled, randomised, 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 COVID-19 mRNA vaccine clinical development program:

- 21,937 participants were exposed to COVID-19 mRNA vaccine, including 96 participants from study BNT162-01.

- 21,797 participants were exposed to Placebo (none from study BNT162-01).

Exposure to COVID-19 mRNA vaccine for participants aged 16 years and older in the 2 ongoing studies by number of doses, and demographic characteristics is shown in Table 9 through Table 19.

In addition, exposure in clinical studies in special populations is provided in Table 25.

Participants 12 to 15 years of age

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

In this study, a total of 2260 participants 12- to 15 years of age were vaccinated in the COVID-19 mRNA vaccine clinical development:

- 1124 participants received 2 doses and 7 received 1 dose of COVID-19 mRNA vaccine in the Blinded-Placebo Controlled Follow-up period;

- 1129 participants received placebo (of these 49, then received 1 dose of COVID-19 mRNA vaccine in the Open-Label Follow-up period after unblinding).

Exposure to COVID-19 mRNA vaccine for participants aged 12- to 15 years of age by number of doses and demographic characteristics is shown in Table 20 through Table 24. Note: Data for 12- to 15 years of age at the cut-off date of 14 November 2020 are shown in Table 11, while data for 12- to 15 years of age at the cut-off date of 13 March 2021 are displayed in Table 20 through Table 24.

In addition, exposure in clinical studies in special populations is provided in Table 26 and Table 27.

Table 9. 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

Table 9. 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
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.
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_s912

Table 10. Exposure to BNT162b2 by Age Group and Dose (BNT162-01)

Age Group Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
≥18 years to ≤55 years		
Vaccine 1 µg		
1 Dose	1	1
2 Doses	11	22
Total	12	23
Vaccine 3 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24
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

Table 10. Exposure to BNT162b2 by Age Group and Dose (BNT162-01)

Age Group Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 30 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24
>55 years		
Vaccine 1 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 3 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 10 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24

Table 10. Exposure to BNT162b2 by Age Group and Dose (BNT162-01)

Age Group Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 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

Table 11. 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

Table 12. Exposure to BNT162b2 by Dose (Totals) (C4591001)

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

Table 13. Exposure to BNT162b2 by Dose (Totals) (BNT162-01)

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

Table 13. Exposure to BNT162b2 by Dose (Totals) (BNT162-01)

Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 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

Table 14. Exposure to BNT162b2 by Dose, Age Group, and Gender (C4591001)

Dose Age Group	Number of Subjects Exposed to BNT162b2 Male	 Female	Total Number of Vaccine Doses 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.
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_s932

Table 15. 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

Table 15. 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 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

Table 16. 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
≥16 years to ≤17 years		
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
≥18 years to ≤55 years		
Vaccine 10 µg		
Racial Origin		
White	11	22
Asian	1	2
Total	12	24
Ethnic Origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	11	22
Total	12	24

Table 16. 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 20 µg		
Racial Origin		
White	10	20
Black or African American	2	4
Total	12	24
Ethnic Origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	11	22
Total	12	24
Vaccine 30 µg		
Racial Origin		
White	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

Table 16. 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
Not reported	64	121
Total	12655	24485
>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
Vaccine 30 µg		
Racial Origin		
White	7842	15403
Black or African American	671	1312

Table 16. 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
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

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
≥18 to ≤55 years		
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

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

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

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

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

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
≥18 to ≤55 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

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
≥18 to ≤55 years		
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

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

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

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

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

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

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

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

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

Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
>55 to ≤85 years		
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

PFIZER CONFIDENTIAL SDTM Creation: 03NOV2020 (21:23) Source Data: adsl Table Generation: 17NOV2020 (12:53) (Cutoff date:02OCT2020, Snapshot Date: 02OCT2020)
Output File: ex_b2_age_dose_race.rtf

Table 18. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001)

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

Table 18. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001)

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
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 19. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 1 µg		
Racial Origin		
White	12	23
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

Table 19. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

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

Table 19. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

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

Table 19. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

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

Table 19. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

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

Table 20. Exposure to BNT162b2 (C4591001) – All Subjects 12-15 Years – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥12 years to ≤15 years		
Vaccine 30 µg		
1 Dose	7	7
2 Doses	1124	2248
Total	1131	2255

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 (14:39)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s914

Table 21. 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

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥12 years to ≤15 years[a]		
Vaccine 30 µg		
1 Dose	30	30
2 Doses	19	38
Total	49	68

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: 01APR2021 (17:33)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s915

Table 22. Exposure to BNT162b2 by Gender (C4591001) – All Subjects 12-15 Years – Blinded Placebo-Controlled Follow-up Period

	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses	
Dose Age Group	Male	Female	Male	Female
Vaccine 30 µg				
≥12 years to ≤15 years	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: 01APR2021 (18:25)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s9324

Table 23. Exposure to BNT162b2 by Race/Ethnic Origin (C4591001) – All Subjects 12-15 Years – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥12 years to ≤15 years		
Vaccine 30 µg		
Racial origin		
White	971	1937
Black or African American	52	103
Asian	72	143
American Indian or Alaska Native	4	8
Native Hawaiian or other Pacific Islander	3	6
Multiracial	23	46
Not reported	6	12
Total	1131	2255
Ethnic origin		
Hispanic/Latino	132	263
Non-Hispanic/non-Latino	997	1988
Not reported	2	4
Total	1131	2255

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 24. 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

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥12 years to ≤15 years[a]		
Vaccine 30 µg		
Racial origin		
White	45	62
Asian	3	5
Multiracial	1	1
Total	49	68
Ethnic origin		
Hispanic/Latino	2	4
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: 01APR2021 (19:02)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s944_open

Table 25. Exposure to BNT162b2 (30 µg) by Special Population (C4591001)

Population	Number of Subjects Exposed to BNT162b2 (30 µg) (N[a]= 21720) n[b]	Total Number of Vaccine Doses
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

Table 25. Exposure to BNT162b2 (30 µg) by Special Population (C4591001)

Population	Number of Subjects Exposed to BNT162b2 (30 µg) (N[a]= 21720) n[b]	Total Number of Vaccine Doses
Peptic Ulcer Disease	62	120
Obese (≥30.0 kg/m^2)	7488	14593

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 in the specified group.
b. n = Number of subjects reporting at least 1 occurrence of any comorbidity or BMI (≥30.0 kg/m^2)..
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

Table 26. Exposure to BNT162b2 (30 µg) by Special Population (C4591001) – All Subjects 12-15 years – Blinded Placebo-Controlled Follow-up Period

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

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 ≥95th percentile [12-15 Years of age]).
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:25) Source Data: admh Table Generation: 27MAR2021 (12:47)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/admh_s953_12

Table 27. 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

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

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 ≥95th percentile [12-15 Years of age]).
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:25) Source Data: admh Table Generation: 27MAR2021 (12:47)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/admh_s953_121

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Detailed descriptions of all inclusion and exclusion criteria for clinical studies are provided in the individual CSRs.

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 hospitalisation for worsening disease during the 6 weeks before enrolment, 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 Section 10.8 of C4591001 protocol.

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

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

Exclusion criteria

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

- **Previous vaccination with any coronavirus vaccine**

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

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

  Rationale: Minimal potential clinical impact on the target population.

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

  Reason for exclusion: Phase 1 excluded participants with a previous clinical or microbiological diagnosis of COVID-19 because these participants may have some degree of protection from subsequent infection by SARS-CoV-2 and therefore would confound the pivotal efficacy endpoint. During Phase 2/3, participants with prior

undiagnosed infection were allowed to be enrolled. Screening for SARS-CoV-2 with nucleic acid amplification test by nasal swab or antibodies to non-vaccine SARS-CoV-2 antigen by serology was not conducted before vaccine administration in Phase 2/3, but samples were taken to run these assays after vaccination, thus identifying participants with unidentified prior infection. This group will be assessed to identify whether prior infection affects safety.

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

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

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

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

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

  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 COVID-19 mRNA vaccine would have unexpected negative consequences to the embryo or foetus.

- **Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour 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 COVID-19 mRNA vaccine is not expected to differ in these subjects when properly administered.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical studies are limited in size and, therefore, unlikely to detect very rare adverse reactions, or adverse reactions with a long latency.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

There has been limited exposure to COVID-19 mRNA vaccine in some special populations and no epidemiologic studies have been conducted in pregnant/breastfeeding women, paediatric participants (<12 years of age), and specific subpopulations that were excluded from the COVID-19 mRNA vaccine program.

Table 28. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Available data on COVID-19 mRNA vaccine administered to pregnant women are insufficient to inform on vaccine-associated risks in pregnancy. Therefore, administration of Comirnaty in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. **Participants 16 years of age and older** Through the cut-off date of 14 November 2020, there were 11 cases (11 events) originating from Study C4591001, and all were unique pregnancies. **Participants 12 to 15 years of age** Through the cut-off date of 13 March 2021, there were no cases of pregnancies.
Breastfeeding women	Breastfeeding women were not included in the COVID-19 mRNA vaccine clinical development program. Data are not available to assess the effects of COVID-19 mRNA vaccine on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COVID-19 mRNA vaccine and any potential adverse effects on the breastfed newborn/infant/toddler from COVID-19 mRNA vaccine or from the underlying maternal condition. For preventive

Table 28. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Breastfeeding women *(cont'd)*	vaccines, the underlying maternal condition is susceptible to disease prevented by the vaccine. **Participants 16 years of age and older** Through the cut-off date of 14 November 2020, there were no CT cases indicative of exposure during breastfeeding. **Participants 12 to 15 years of age** Through the cut-off date of 13 March 2021, there were no CT cases indicative of exposure during breastfeeding.
Participants with relevant comorbidities: • Participants with hepatic impairment • Participants with renal impairment • Participants with cardiovascular disease • Immunocompromised participants • Participants with a disease severity different from inclusion criteria in CTs	Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 6 weeks before enrolment, were included. This allowed enrolment of a proportion of participants with common comorbidities such as cardiovascular diseases including hypertension, chronic pulmonary diseases, asthma, chronic liver disease, BMI >30 kg/m^2, participants with stage 3 or worse chronic kidney disease, and participants with varying disease severity. Participants with potential immunodeficient status were not specifically included in the study population. **Participants 16 years of age and older** Please refer to Table 25 for the exposure of special populations. **Participants 12 to 15 years of age** Please refer to Table 26 and Table 27 for the exposure of special populations.
Population with relevant different ethnic origin	Please refer to Table 16 to Table 19 for exposure information by ethnic origin from the studies.
Subpopulations carrying relevant genetic polymorphisms	No data available.
Paediatric participants	The safety and efficacy in paediatric subjects aged less than 12 years of age have not yet been established. Limited data are available. **Participants 12 to 15 years of age** One thousand a hundred eighty (1180) paediatric participants 12 to 15 years of age received COVID-19 mRNA vaccine through the cut-off date of 13 March 2021 (Table 20 and Table 21).
Elderly (≥65 years old)	**Participants 16 years of age and older** Clinical studies of COVID-19 mRNA vaccine included 4580 participants 65 years of age and over through the cut-off date of 14 November 2020 (Table 11).

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; CT = clinical trial.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

It is not possible to determine with certainty the number of individuals who received COVID-19 mRNA vaccine since it was first authorised 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 28 February 2021, approximately 126,212,580 doses of COVID-19 mRNA vaccine were shipped worldwide. The estimated cumulative number of shipped doses of COVID-19 mRNA vaccine by region, are summarised in Table 29.

Table 29. Cumulative Estimated Shipped Doses[a] of COVID-19 mRNA Vaccine by Region Worldwide

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

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

SV.1.1. Method Used to Calculate Exposure

Not applicable.

SV.1.2. Exposure

Not applicable.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

COVID-19 mRNA vaccine does not have characteristics that would make it attractive for use for illegal purposes; therefore, there is only a low potential for COVID-19 mRNA vaccine misuse for illegal purposes.

Module SVII. Identified and Potential Risks

In accordance with EMA RMP guidance for COVID-19 vaccines, the below factors were taken into consideration for the generation of the safety specification and are not determined to be identified or potential risks.

- **The vaccine construct and the formulation**. The COVID-19 mRNA vaccine consists of non-infectious, non-replicating RNA in a lipid-based formulation, which delivers the RNA to cells in the immunised person. Protein expression from the RNA is transient, and as is RNA itself. There is no toxicity associated with the LNP or its metabolism (Study reports 38166 and 20GR142). Vacuolation of hepatocytes was observed in rat toxicity studies and believed to be associated with the uptake of the LNP and was without evidence of any effect on liver function. The liver vacuolation was reversed approximately 3-weeks after the last administration.

- **The degradation of the active substance / antigen and potential impact on safety related to this; (e.g. for mRNA-based vaccines).** Like endogenous mRNA in the cytosol, vaccine RNA in cytosol is degraded. The COVID-19 mRNA contains no known toxic products of the degradation of the RNA or the lipids in the formulation.

- **The vaccine does not contain an adjuvant**.

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The safety concerns of COVID-19 mRNA vaccine in the initial RMP are listed in Table 30.

Table 30. Summary of 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 while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

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 RMP.

Reasons for not including an identified or potential risk in the list of safety concerns in this RMP include:

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

The following reactogenicity events are identified risks not considered as Important: Injection site pain, Injection site swelling and Injection site redness, Fever, Chills, Fatigue, Headache, Muscle pain, and Joint pain.

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

In acknowledgment of the EMA core RMP19 guidance, the reactogenicity profile of COVID-19 mRNA vaccine is discussed below with respect to observed differences in solicited reactogenicity systemic events between Dose 1 and Dose 2. The observed differences do not impact the safety profile of the vaccine and are not proposed to be included in the list of safety concerns, rather they are discussed for completeness in the presentation of the safety profile.

Reactogenicity

At the time of the safety cut-off date (14 November 2020), the Phase 2/3 reactogenicity subset comprised 8183 participants (≥12 years of age), which included the 360 participants in Phase 2. The reactogenicity data were collected by participants' e-diary for reporting prompted local reactions and systemic events for 7 days after each dose. Adolescents 12 to 15 years of age were analysed in a separate group; these are preliminary data provided in support of the indication which was initially for ≥16 years of age.

- ***Local Reactions***

In the BNT162b2 group, pain at the injection site was reported more frequently in the younger group (16-55 years) than in the older group (> 55 years), and frequency was similar after Dose 1 compared with Dose 2 of BNT162b2 in the younger group (83.1% vs 77.8%) and in the older group (71.1% vs 66.1%).

In the BNT162b2 group, frequencies of redness and swelling were similar in the younger and older age group after Doses 1 and 2. Frequencies of redness were similar after Dose 1 compared with Dose 2 of BNT162b2 in the younger age group (4.5% vs 5.9%) and in the older age group (4.7% vs 7.2%). Frequencies of swelling were similar after Dose 1 compared with Dose 2 of BNT162b2 in the younger age group (5.8% vs 6.3%, respectively) and in the older age group (6.5% vs 7.5%). In the placebo group, redness and swelling were reported infrequently in the younger (≤1.1%) and older (≤1.1%) groups after Doses 1 and 2.

Overall, across age groups, pain at the injection site did not increase after Dose 2, and redness and swelling were generally similar in frequency after Dose 1 and Dose 2. Most local reactions were mild or moderate in severity. Few severe local reactions were reported

after either dose. The frequency of any severe local reactions after Dose 1 and after Dose 2 was ≤0.6%. No grade 4 (potentially life-threatening) reactions were reported.

Across age groups, local reactions for the BNT162b2 group after either dose had a median onset day between Day 1 and Day 3 (Day 1 was the day of vaccination) and ranges were similar in the younger and older age groups. Across age groups, local reactions for this group after either dose resolved with median durations between 1 to 2 days, which were similar in the younger and older age groups.

No clinically meaningful differences in local reactions were observed by age and/or or baseline SARS-CoV-2 status subgroups.

- **Systemic Events**

Systemic events were generally increased in frequency and severity in the younger age group (16-55 years) compared with the older age group (> 55 years), with frequencies and severity increasing with number of doses (Dose 1 vs Dose 2). Vomiting and diarrhoea were exceptions, with vomiting reported similarly infrequently in both age groups and diarrhoea reported at similar incidences after each dose.

Systemic events in the younger group compared with the older group, with frequencies increasing with number of doses (Dose 1 vs Dose 2), were:

- fatigue: younger group (47.4% vs 59.4%) compared to older group (34.1% vs 50.5%)
- headache: younger group (41.9% vs 51.7%) compared to older group (25.2% vs 39.0%)
- muscle pain: younger group (21.3% vs 37.3%) compared to older group (13.9% vs 28.7%)
- chills: younger group (14.0% vs 35.1%) compared to older group (6.3% vs 22.7%)
- joint pain: younger group (11.0% vs 21.9%) compared to older group (8.6% vs 18.9%)
- fever: younger group (3.7% vs 15.8%) compared to older group (1.4% vs 10.9%)
- vomiting: reported less frequently in the older group and was similar after either dose
- diarrhoea: reported less frequently in the older group and was similar after each dose.

Systemic events were generally reported less frequently in the placebo group than in the BNT162b2 group, for both age groups and doses, with some exceptions. In the younger age group, vomiting and diarrhoea (after Dose 1 and Dose 2) were reported at similar frequencies in the placebo group and the BNT162b2 group. In the older age group, fever and joint pain (after Dose 1) and vomiting and diarrhoea (after Dose 1 and Dose 2) were reported at similar frequencies in the placebo group and the BNT162b2 group.

Following both Dose 1 and Dose 2, use of antipyretic/pain medication was slightly less frequent in the older age group (19.9% vs 37.7%) than in the younger age group (27.8% vs 45.0%) after both doses, and medication use increased in both age groups after Dose 2 as compared with after Dose 1. Use of antipyretic/pain medication was less frequent in the placebo group than in the BNT162b2 group and was similar after Dose 1 and Dose 2 in the younger and older placebo groups (9.8% to 22.0%).

After the first and second dose and in both age groups, the majority of systemic events were mild or moderate in severity. Systemic events across age groups after Dose 1 of BNT162b2 were generally lower in frequency than after Dose 2: fever (2.7% vs 13.6%), fatigue (41.5% vs 55.5%), headache (34.5% vs 46.1%), chills (10.6% vs 29.6%), muscle pain (18.0% vs 33.5%), and joint pain (9.9% vs 20.5). Diarrhoea and vomiting frequencies were generally similar. The frequency of any severe systemic event after Dose 1 was ≤0.9%. After Dose 2, systemic events had frequencies of < 2% with the exception of fatigue (3.8%) and headache (2.0%).

In the placebo group, severe fever was reported at a similar frequency (≤0.4%) after Dose 1 and Dose 2. One participant in the younger BNT162b2 group reported fever of 41.2°C only on Day 2 after Dose 2 and was nonfebrile for all other days of the reporting period. One other participant in the younger group reported fever that reached a high temperature of 42.3°C on Day 4 after Dose 1 that lasted in total for 3 days; the participant was nonfebrile at the end of the reporting period.

Across age groups, median onset day for most systemic events after either dose of BNT162b2 was Day 2 to Day 3 (Day 1 was the day of vaccination), and ranges were similar in the younger and older age groups. Across age groups, all systemic events resolved with median duration of 1 day, which was similar in the younger and older age groups.

Other than fatigue and headache, most systemic events were infrequent in placebo recipients.

Antipyretic/pain medication use in the younger adolescent group was modestly increased after Dose 2 compared to Dose 1 (30.6% vs 41.3%) and was greater than use in the placebo group (9.8% vs 13%).

No clinically meaningful differences in systemic events were observed by age and/or baseline SARS-CoV-2 status subgroups. In summary, increases in some systemic reactogenicity events (fever, chills, headache, fatigue, muscle pain and joint pain) were observed in the week following Dose 2 when compared with the week following Dose 1. The differences are small enough that they are unlikely to discourage vaccinees from completing the full 2-dose regimen for vaccination neither do they impact the benefit risk profile of the vaccine overall. Overall, the reactogenicity events have only temporary clinical impact on patients in relation to the potential severity of the disease prevented.

Adverse Events of Special Interest (AESI)

COVID-19 mRNA vaccine study C4591001 did not pre-specify AESI however, Pfizer utilizes a dynamic list of TME terms to be highlighted in clinical study safety data review. TMEs include events of interest due to their association with COVID-19 and terms of interest for vaccines in general and may include Preferred Terms, High Level Terms, High Level Group Terms or Standardised MedDRA Queries.

For the purpose of the RMP and summary safety reports, an AESI list was composed taking into consideration the available lists of AESIs from the following expert groups and regulatory authorities:

Brighton Collaboration (SPEAC)[61]

- ACCESS protocol[62]
- US CDC (preliminary list of AESI for VAERS surveillance)[63]
- MHRA (unpublished guideline).

The AESI list is comprised of medical conditions to allow for changes and customisation of MedDRA terms as directed by AE reports and the evolving safety profile of the vaccine:

- Immune/Autoimmune-mediated neurological, haematological and vasculitis events;
- Events associated with severe COVID-19;
- Serious thrombotic and embolic events.

The AESIs are taken in consideration for all routine and additional pharmacovigilance activities.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Anaphylaxis

Risk-benefit impact

Anaphylaxis is a serious adverse reaction that, although very rare, can be life-threatening.

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

Risk-benefit impact

Although not observed or identified in clinical studies with COVID-19 vaccines, there is a theoretical risk, mostly based on non-clinical betacoronavirus data, of VAED occurring either before the full vaccine regimen is administered or in vaccinees who have waning immunity over time. If VAED were to be identified as a true risk, depending on its incidence and severity, it may negatively impact the overall vaccine benefit risk assessment for certain individuals.

Missing Information: Use in Pregnancy and while breast feeding

Risk-benefit impact

The safety profile of the vaccine is not known in pregnant or breastfeeding women due to their exclusion from the pivotal clinical study. Accordingly, maternal COVID-19 impact to either embryo or foetus is also not known. It is important to obtain long term follow-up on women who were pregnant at or around the time of vaccination so that any potential negative

consequences to the pregnancy can be assessed and weighed against the effects of maternal COVID-19 on the pregnancy.

Missing Information: Use in immunocompromised patients

Risk-benefit impact

The safety profile of the vaccine is not known in immunocompromised individuals due to their exclusion from the pivotal clinical study. The efficacy of the vaccine may be lower in immunocompromised individuals, thus decreasing their protection from COVID-19.

Missing Information: Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Risk-benefit impact

There is limited information on the safety of the vaccine in frail patients with co-morbidities who are potentially at higher risk of severe COVID-19.

Missing Information: Use in patients with autoimmune or inflammatory disorders

Risk-benefit impact

There is limited information on the safety of the vaccine in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.

Missing Information: Interaction with other vaccines

Risk-benefit impact

BNT162b2 mRNA vaccine will be used in individuals who also may receive other vaccines. Studies to determine if co-administration of BNT162b2 mRNA vaccine with other vaccines may affect the efficacy or safety of either vaccine have not been performed.

Missing Information: Long term safety data

Risk-benefit impact

The long-term safety of BNT162b2 mRNA vaccine is unknown at present, however further safety data are being collected in ongoing Study C4591001 for up to 2 years following administration of dose 2 of BNT162b2 mRNA vaccine.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risk: Anaphylaxis

Table 31. Anaphylaxis

Potential mechanisms, evidence source and strength of evidence	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 dyspnoea, hypotension, swelling (sometimes leading to airway compromise), and rash (including hives).
Characterisation of the risk	***Participants 16 years of age and older*** Data from the CT database: Data from the ongoing Phase 3 clinical Study C4591001 through the cut-off date of 14 November 2020 have been reviewed and information pertinent to anaphylactic reactions observed in the study is summarised below. Two (2) serious events (Anaphylactic reaction and Anaphylactic shock) were reported. Anaphylactic reaction due to a bee sting in a BNT162b2 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. Data from the safety database: 2 serious events (Anaphylactic reaction and Anaphylactoid reaction) were reported during the emergency use authorisation. ***Participants 12 to 15 years of age***[a] Data from the CT database 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. Data from the safety database: Through 28 February 2021, there were no cases reporting anaphylactic reactions in the safety database in the 12 to 15 years of age participants.
Risk factors and risk groups	Known hypersensitivity to any components of the vaccine.
Preventability	Prevention of anaphylaxis may not be possible, particularly with the 1st dose of a vaccine; therefore, healthcare professionals administering the vaccine must be vigilant for early signs and symptoms.
Impact on the risk-benefit balance of the biologic product	Anaphylactic reaction in an individual can be impactful (medically important) because it is a potentially life-threatening event requiring medical intervention.
Public health impact	Anaphylactic reaction in an individual can be impactful (medically important) because it is a potentially life-threatening event requiring medical intervention.

a. Search criteria for cases of anaphylaxis in the safety database have been revised as compared to RMP version 1.0. The new search criteria are: Anaphylactic reaction SMQ (Narrow and Broad, with the MedDRA algorithm applied), with relevant cases assessed according to Brighton Collaboration (BC) criteria.

SVII.3.1.2.Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Table 32. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Potential mechanisms, evidence source and strength of evidence

This potential risk is theoretical because it has not been described in association with the COVID-19 mRNA 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 immunisation, 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.[56,64] 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.[65]

Potential mechanisms of enhanced disease may include both T cell-mediated [an immunopathological response favouring T helper cell type 2 (Th2) over T helper cell type 1 (Th1)] and antibody-mediated immune responses (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).[66]

Characterisation 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[a]=21721) n[b] (%)	BNT162b2 (30 µg) (N[a]=21721) (95% CI[c])	Placebo (N[a]=21729) n[b] (%)	Placebo (N[a]=21729) (95% CI[c])
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[d]	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

Table 32. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

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 unfavourable imbalance in severe COVID-19 cases in vaccinated individuals when compared to those not vaccinated. It is challenging to assess for VAED/VAERD on an individual case basis, given the lack of specific clinical or laboratory markers at this time, rather surveillance for this theoretical risk is best performed at a population level,[67] as noted above. The table above shows a favourable balance of severe COVID-19 cases in participants receiving COVID-19 mRNA vaccine versus those receiving placebo, providing reassurance against the potential risk of VAED/VAERD at this time.

Participants 12 to 15 years of age[a]

Data from the CT database

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

Confirmed Case of Postvaccination Severe COVID-19 – All Subjects 12-15 Years – Blinded Placebo-Controlled Follow-up Period – Safety Population (C4591001)

	BNT162b2 (30 µg) (N[a]=1131)		Placebo (N[a]=1129)	
Timing	**n[b] (%)**	**(95% CI[c])**	**n[b] (%)**	**(95% CI[c])**
PD1 Before Dose 2	0	(0.0, 0.3)	0	(0.0, 0.3)
Within 7 days PD1	0	(0.0, 0.3)	0	(0.0, 0.3)
PD2	0	(0.0, 0.3)	0	(0.0, 0.3)
Total[d]	0	(0.0, 0.3)	0	(0.0, 0.3)

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 that appeared to be cases of VAED or VAERD in the safety database involving the 12 to 15 years of age participants.

Risk factors and risk groups	It is postulated that the potential risk may be increased in individuals producing lower neutralizing antibody titers or in those demonstrating waning immunity.[66,67]
Preventability	An effective vaccine against COVID-19 that produces high neutralizing titers and a Th1 predominant $CD4^+$ T cell response and strong $CD8^+$ T cell response, is expected

Table 32. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

	to mitigate the risk of VAED/VAERD;[56,66] that immune profile is elicited by BNT162b2 in clinical and preclinical studies.[68,69]
Impact on the risk-benefit balance of the biologic product	If there were an unfavourable balance in COVID-19 cases, including severe cases, in the pivotal clinical study between the vaccine and placebo groups, that may signal VAED/VAERD.
Public health impact	The potential risk of VAED/VAERD could have a public health impact if large populations of individuals are affected.

a. Search criteria for cases of potential VAED have been revised as compared to RMP version 1.0. The new search criteria are: Standard Decreased Therapeutic Response Search AND at least 1 of the following PTs Dyspnoea; Tachypnoea; Hypoxia; COVID 19 pneumonia; Respiratory Failure; Acute Respiratory Distress Syndrome; Cardiac Failure; Cardiogenic shock; Acute myocardial infarction; Arrhythmia; Myocarditis; Vomiting; Diarrhoea; Abdominal pain; Jaundice; Acute hepatic failure; Deep vein thrombosis; Pulmonary embolism; Peripheral Ischaemia; Vasculitis; Shock; Acute kidney injury; Renal failure; Altered state of consciousness; Seizure; Encephalopathy; Meningitis; Cerebrovascular accident; Thrombocytopenia; Disseminated intravascular coagulation; Chillblains; Erythema multiforme; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome in children;

Note: the "Standard Decreased Therapeutic Response" search include the Lack of efficacy PTs (Drug ineffective/Vaccination failure).

SVII.3.2. Presentation of the Missing Information

Table 33. Use in pregnancy and while breast feeding

Evidence source:
The safety profile of the vaccine is not known in pregnant or breastfeeding 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 favourable or unfavourable impacts on the embryo/foetus. The clinical consequences of SARS-CoV-2 infection to the woman and foetus 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. 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 characterisation:
The lack of data will be communicated in product labelling; a clinical study of the safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women, is planned.

Table 34. Use in immunocompromised patients

Evidence source:
The vaccine has not been studied in individuals with overt immunocompromised conditions. Therefore, further safety data will be sought in this population.

Population in need of further characterisation:
Safety data will be collected in individuals with compromised immune function due to acquired or genetic conditions or conditions requiring the use of immunosuppressants as this population of individuals in the active surveillance studies and the clinical studies proposed by the MAA (see Section PART III).

Table 35. Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Evidence source:
The vaccine has been studied in individuals with stable chronic diseases (e.g. hypertension, obesity), however it has not been studied in frail individuals with severe co-morbidities that may compromise immune function due to the condition or treatment of the condition. Therefore, further safety data will be sought in this population.

Population in need of further characterisation:
Safety data will be collected in individuals who are frail due to age or debilitating disease in the active surveillance studies and through routine pharmacovigilance.

Table 36. Use in patients with autoimmune or inflammatory disorders

Evidence source:
There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders.

Population in need of further characterisation:
Safety data will be collected in individuals with autoimmune or chronic inflammatory diseases, including those who may be on immunosuppressants in the active surveillance studies.

Table 37. Interaction with other vaccines

Evidence source:
There are no data on interaction of BNT162b2 mRNA vaccine with other vaccines at this time.

Population in need of further characterisation:
All reports describing interactions of COVID-19 vaccine with other vaccines per national recommendations in individuals will be collected and analysed as per routine PV activities. Interactions with commonly used non-COVID-19 vaccines, such as influenza vaccine, are proposed to be studied in a future clinical study.

Table 38. Long term safety data

Evidence source:
At this time, 2-month post dose 2 safety data are available for approximately half of the patients who have received BNT162b2 mRNA vaccine in Study C4591001. The study is ongoing.

Anticipated risk/consequence of missing information:
At the time of vaccine availability, the long-term safety of BNT162b2 mRNA vaccine is not fully known, however there are no known risks with a potentially late onset. Data will continue to be collected from participants in ongoing study C4591001 for up to 2 years following the 2nd dose of vaccine. Additionally, active surveillance studies are planned to follow long-term safety in vaccine recipients for 2 years following Dose 2.

Module SVIII. Summary of the Safety Concerns

Table 39. Summary of 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 while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities for the lifecycle of a product is a critical component to the detection, assessment, understanding and mitigation of risks. Objectives of routine pharmacovigilance includes having processes in place to assure the ongoing and timely collection, processing, follow-up, and analysis of individual AE reports and aggregate data globally, following global safety Standard Operating Procedures and regulatory guidance.

Pfizer, on behalf of the MAA monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant safety information is conveyed in a timely manner to regulatory authorities and other interested parties as appropriate and in accordance with international principles and prevailing regulations. Pfizer, on behalf of the MAA, gathers data for signal detection and evaluation commensurate with product characteristics.

Routine pharmacovigilance activities beyond the receipt and review of individual AE reports (e.g. ADRs) include:

- Data Capture Aids have been created for this vaccine. 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. The DCA is provided in Annex 4;
  - potential anaphylactic reactions in individuals who have received the COVID-19 mRNA vaccine. This DCA is in preparation and will be submitted.
- Signal detection activities for the lifecycle of vaccines consist of individual AE assessment at case receipt, regular aggregate review of cases for trends and statistically disproportionately reported product-adverse event pairs. Aggregated and statistical reviews of data are conducted utilizing Pfizer's software interactive tools. Safety signal evaluation requires the collection, analysis and assessment of information to evaluate potential causal associations between an event and the product and includes subsequent qualitative or quantitative characterisation of the relevant safety risk to determine appropriate continued pharmacovigilance and risk mitigation actions. Signal detection activities for the COVID-19 mRNA vaccine, will occur on a weekly basis. In addition, observed versus expected analyses will be conducted as appropriate as part of routine signal management activity.
- Routine signal detection activities for the COVID-19 mRNA vaccine will include routine and specific review of AEs consistent with the AESI list provided in PART II.SVII.1.1 – *Risks not considered important for inclusion in the list of safety concerns in the RMP*.
- In addition, published literature is reviewed weekly for individual case reports and broader signal detection purposes.

- Regulatory authority safety alerts monitoring.
- A web-based AE reporting portal will be available for vaccine providers (e.g. pharmacists, nurses, physicians and others who administer vaccines) and recipients, to assist with anticipated high volume of reports (based on expectations of a large target population for vaccination). 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 Pfizer Drug Safety Units perform 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.
- The serious adverse event (SAE)/product complaint (PC) Joint Report for Sterile Injectables is run monthly. In addition, the AE/PC Joint report and the AE/PC Lot/Lot profile Report is run quarterly and is a statistical report that identifies any data that could constitute a safety signal over time. The AE/PC Lot/Lot Profile report complements the monthly AE trending performed by Safety and the monthly PC trending performed by Product Quality.

Monthly summary safety reports

In addition to routine 6-monthly PSUR production, monthly summary safety reports are compiled to support timely and continuous benefit risk evaluations. Topics covered by monthly summary safety reports include:

- Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately);
- Interval and cumulative number of reports, overall and by age groups and in special populations (e.g. pregnant women);
- Interval and cumulative number of reports per HLT and SOC;
- Summary of the designated medical events;
- Reports per EU country;
- Exposure data (including age-stratified);
- Changes to reference safety information in the interval, and current CCDS;
- Ongoing and closed signals in the interval;
- AESI reports – numbers and relevant cases;
- Fatal reports – numbers and relevant cases;
- Risk/benefit considerations.

The submission of monthly reports complements the submission of 6 monthly PSURs. The need and frequency of submission of such reports will be re-evaluated based on the available evidence from post-marketing after 6 months (6 submissions).

- Monthly reports and PSURs will include results of the observed versus expected analysis for AESI as appropriate, including cases of Bell's palsy and will present the results and details of the statistical approach.

Potential Medication Errors

Large scale public health approaches for mass vaccination may represent changes to standard vaccine treatment process, thereby potentially introducing the risk of medication errors related to: reconstitution and administration, vaccination scheme, storage conditions, errors associated with a multi-dose vial, and once other COVID vaccines are available, confusion with other COVID vaccines. These potential medication errors are mitigated through the information in the SmPC and available educational materials for healthcare providers.

- SmPC (section 6.6) contains instructions for reconstitution and administration, vaccination scheme, and storage conditions of the COVID-19 mRNA vaccine.
- A poster with step-by-step instruction for vaccine storage, dose planning and preparation, and administration is available, which can be conspicuously displayed in settings where vaccine is to be administered for ongoing reference.
- Brochures for safe handling of the vaccine and dry ice will accompany vaccine shipments.
- Medical information call centers will be available for healthcare providers to obtain information on use of the vaccine.
- Traceability and Vaccination Reminder card (Annex 7) will be provided with the pre-printed manufacturer name, placeholder spaces for dates of vaccinations and batch/lot numbers as a mitigation effort for potential confusion between vaccines. (see Traceability for additional details).

These available resources will inform healthcare providers on the proper preparation and administration of the vaccine and reduce the potential for medication error in the context of a mass vaccination campaign. Additionally, the patient information leaflet and Traceability and Vaccination Reminder card informs patients of the vaccine received so that a series is completed with the same product.

Traceability

The SmPC, includes instructions for healthcare professionals:

- to clearly record the name and batch number of the administered vaccine to improve traceability (section 4.4);
- to report any suspected adverse reactions including batch/Lot number if available (section 4.8).

Traceability is available for every shipping container of COVID mRNA vaccine, which are outfitted with a unique device that provides real-time monitoring of geographic location and temperature 24 hours per day, 7 days per week. Each device will also trace the batch/lot of the associated shipment. The device is activated prior to shipment and information is transmitted wirelessly to Pfizer at a predefined cadence, on behalf of the MAA, until delivery to the vaccinator's practice site. A shipment quality report that indicates if the product is acceptable for immediate use is generated by Pfizer on behalf of the MAA and transmitted to

the vaccinator's practice site upon pressing of the stop button on the data logger, or arrival notification from the carrier in combination with the data loggers location and/or light signal. Additionally, alarms and escalation/notification for excursions (per pre-defined specifications) are programmed into the device. These data may be used for the assessment of a safety signal.

The vaccine carton labelling also contains a 2-D barcode which has the batch/lot and expiry embedded within, should there be capability at a vaccination site to utilize this as an information source.

Further, Pfizer on behalf of the MAA, provides Traceability and Vaccination Reminder cards (Annex 7) to vaccinators that may be completed at the time of vaccination. The Traceability and Vaccination Reminder cards contain the following elements:

- Placeholder space for name of vaccinee;
- Vaccine brand name and manufacturer name;
- Placeholder space for due date and actual date of first and second doses, and associated batch/lot number;
- Reminder to retain the card and bring to the appointment for the second dose of the vaccine;
- QR code that links to additional information; and
- Adverse event reporting information.

In addition, to the Traceability and Vaccination Reminder cards, two stickers per dose, containing printed batch/lot information, will be made available to support documentation of the batch/lot on the Traceability and Vaccination Reminder card and vaccinee medical records in mass vaccination centers. We also acknowledge that some EU member states may require utilisation of nationally mandated vaccination cards or electronic systems to document batch/lot number; therefore, the available Traceability and Vaccination Reminder cards and stickers with printed lot/batch information may not be utilised in all member states. The following milestones are proposed for the availability of the stickers with printed lot/batch information:

- Initial vaccine availability: Sufficient quantities of blank "Traceability and Vaccination Reminder cards" will be made available to vaccinators in the member states where utilisation of a nationally mandated vaccination card is not required.
- 31 January 2021: In addition to the blank "Traceability and Vaccination Reminder cards", stickers with printed lot/batch information were made available to vaccinators at large scale (1000 subjects/day), mass vaccination sites in the member states where the national authority has not mandated another mechanism for documenting the lot/batch information.
- Projected 2022: Upon development and approval a of single-dose vials, pre-printed batch/lot stickers will be available to co-ship with each vaccine shipment.

Cold-Chain Handling and Storage

Multiple modalities will be utilised for quality assurance throughout shipment due to the required ultra-cold storage for COVID-19 mRNA vaccine.

- Each shipment of the vaccine is outfitted with a unique device that provides real-time monitoring of geographic location and temperature 24 hours per day, 7 days per week until delivery to a vaccinator's practice site. Alarms and escalation/notification to Pfizer on behalf of the MAA and/or to the recipient for excursions (per pre-defined specifications) are programmed into the device. Additionally, a shipment quality report that indicates if the product is acceptable for immediate use is generated by Pfizer and transmitted to the vaccinator's practice site.
- Joint adverse event and product complaint (including available batch/lot information) trending reviews occur routinely with Global Product Quality.
- Additionally, available educational materials for vaccinators will include information regarding proper handling of the shipment container as temporary storage, and handling/disposal of dry ice until the received shipment is either placed into an ultra-low temperature freezer, or is maintained in accord with pre-defined specifications in the shipment container as temporary storage (i.e. upon receipt of the shipment quality report noted above), as appropriate.

III.2. Additional Pharmacovigilance Activities

The MAA proposes the following 13 studies, of which 1 global, 4 in Europe only, 1 in Europe and US, and 5 in US only; the countries where 2 studies are planned to be conducted are not available at this time. There are 6 Interventional studies (C4591001, C4591015, BNT162-01 Cohort 13, C4591018, 1 study in high risk adults and 1 study for vaccine interactions), 1 Low-Interventional study (WI235284) and 6 Non-Interventional studies (4 safety and 2 effectiveness), summarised in the table below and further detailed in Table 40 and Table 41.

Study Number	Country	Interventional/ Non-Interventional	Purpose
C4591001	Global	Interventional	Safety
C4591015	Not available at this time	Interventional	Safety
C4591010	EU	Non-Interventional	Safety
C4591011	US	Non-Interventional	Safety
C4591012	US	Non-Interventional	Safety
ACCESS/VAC4EU	EU	Non-Interventional	Safety
C4591014	US	Non-Interventional	Effectiveness [a]
WI235284	US	Low-Interventional [d]	Effectiveness [a]
WI255886	ex-EU[c]	Non-Interventional	Effectiveness [a]
BNT162-01 Cohort 13	EU	Interventional	Safety
C4591018	US	Interventional	Safety
Safety and immunogenicity in high risk adults [b]	EU, US	Interventional	Safety
Co-administration study with seasonal influenza vaccine	Not available at this time	Interventional	Safety

a. Vaccine effectiveness is not a safety concern.
b. On review of preliminary information from BNT162-01 cohort 13, C4591001 HIV-infected and high-risk populations and C4591018, a further safety and immunogenicity study is anticipated in up to 150 adult subjects with a range of primary immunocompromising conditions and/or receiving immunocompromising treatments or in conditions.
c. United Kingdom.
d. According to article 2 (2)(3) of the Clinical Trials Regulation No 536/2014, the study does not involve any administration of vaccine or other Pfizer products but since a specimen collection procedure is required per protocol, this qualifies this study as 'low-interventional'.

Non-Interventional Post Approval Safety Studies (4)

- The MAA proposes 4 complementary studies of real-world safety of COVID-19 mRNA vaccine that use multiple data sources and study designs. These are described in Table 40 below which includes the proposed post-approval safety studies that will be conducted in the EU and US.

- Study C4591010 will be conducted in the EU using primary data collection to monitor a cohort of vaccinees and evaluate risk of safety events of interest reflecting the AESI list. A draft protocol C4591010 is provided in Annex 2.

- Additionally, Pfizer, on behalf of the MAA, will sponsor one or more PASS using secondary EHR data sources in Europe based on a master surveillance protocol developed through the ACCESS project, which is funded by EMA and conducted via the Vaccine monitoring Collaboration for Europe (VAC4EU) (VAC4EU, 2020). The MAA has initiated a request for proposal with the VAC4EU secretariat. Pfizer on behalf of the MAA, understands that the master protocol is under development with the EMA and notification will be provided once finalised and will provide draft protocols as soon as available.

- In addition to the studies planned for the EU, in support of the US EUA application, Pfizer has submitted to the FDA 2 draft protocols for safety surveillance of COVID-19 mRNA vaccine in populations expected to receive the vaccination under EUA in the US. These studies include:

  – 1 study using secondary data from EHR of active military and their families (C4591011),

  – 1 study using secondary data from EHR of patients included in the Veterans Healthcare Administration system (C4591012).

- The draft protocols for the proposed safety studies in the US (C4591011 and C4591012) are included in Annex 2.

Non-Interventional Post-Approval Safety Studies in Pregnancy

The proposed strategy to assess vaccination during pregnancy will be implemented in 2 stages. It is anticipated that initial use in pregnancy will be subject to local health authority recommendations regarding which individuals should be vaccinated and likely very limited intentional vaccination of pregnant women; therefore, initially this information will derive from 3 of the real-world safety studies (C4591010, C4591011, and ACCESS/VAC4EU), described in Table 40. Study C4591012 is focused on patients in the Veterans Health Administration system and is not expected to capture many pregnancies given the demographics of the source population. The findings from studies' interim analysis (where planned) will inform a strategy to assess pregnancy outcomes as vaccination in pregnancy expands. MAA will consider established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) when developing any pregnancy related study objectives (currently not listed in Table 40 and Table 41).

The MAA agrees that monitoring vaccine safety in pregnant women is critical. Given that a pregnancy registry based on primary data collection is susceptible to non-participation, attrition, small sample size and limited or lack of comparator data, Pfizer, on behalf of the MAA, would like to propose monitoring vaccine safety in pregnancy using electronic health care data, which could be conducted in a representative pregnant woman population exposed to the vaccine and minimize selection bias, follow-up bias, and reporting bias. In addition, internal comparison groups, such as contemporaneous unvaccinated pregnant women or women receiving other vaccine(s) to prevent COVID-19 (if available) could be included.

Post-Approval Effectiveness Studies (3)

Pfizer will conduct, on behalf of the MAA, at least one non-interventional study (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 illness in a real-world setting (C4591014). The effectiveness of COVID-19 mRNA vaccine will be estimated against laboratory confirmed COVID 19 illness requiring admission to the Emergency Department (ED) or hospital where SARS-CoV-2 is identified. This study will allow to determine the effectiveness of Pfizer's vaccine in a real-world setting and against severe disease, and in specific racial, ethnic, and age groups.

In February 2021, Pfizer has submitted to the FDA a Request for Comments and Advice regarding the study C4591014, a non-interventional study (test-negative design) of BNT162b2 vaccine effectiveness. The purpose of the original study C4591014 has been further developed and 2 new vaccine effectiveness epidemiology studies not sponsored by Pfizer (WI235284 and WI255886) have been added. The harmonisation of study definitions across these 3 protocols will allow for data and results comparison across study populations to provide a robust evidence base for evaluating the effectiveness of BNT162b2 following its introduction into the real-world setting.

Table 40. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type ***Study Status***	Rationale and Study Objectives	Study design	Study populations	Milestones	
C4591001 Global	A Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-COV-2 RNA vaccine candidates against COVID-19 in healthy individuals Interventional *Ongoing*	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2	Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.	Healthy men and women 18-55 and 65-85 years of age. Male and female, aged ≥ 12 years of age. Stable chronic conditions including stable treated HIV, HBV and HCV allowed, excluding immunocompromising conditions and treatments.	CSR submission upon regulatory request: CSR submission 6 months post Dose 2: Final CSR submission with supplemental follow-up:	Any time 31-Dec-2021 31-Aug-2023
C4591011 US	Safety Surveillance of the Pfizer COVID-19 Vaccine in the U.S. Department of Defense Population Following Emergency Use Authorization Non-Interventional *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.	Secondary database analysis of observational data to estimate incidence rates of safety events of interest and other clinically significant events in a cohort of active military and their families who receive the COVID-19 mRNA vaccine under EUA in the US	Active military and their families	Interim reports submission: Final CSR submission:	30-Jun-2021 31-Dec-2021 30-Jun-2022 31-Dec-2022 31-Dec-2023

Table 40. Additional Pharmacovigilance Activities

Study Number ***Country (ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
C4591012 US	Post-Emergency Use Authorization Active Surveillance of Adverse Events of Special Interest among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine Non-Interventional *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Secondary database analysis of observational data to estimate incidence rates of safety events of interest and other clinically significant events in a cohort of US veterans who receive the COVID-19 mRNA vaccine under EUA in the US	US Veteran's	Interim reports submission:	30-Jun-2021
						31-Dec-2021
						30-Jun-2022
						31-Dec-2022
					Final CSR submission:	31-Dec-2023
C4591010 EU	A Post-Approval Active Surveillance Safety Study to Monitor Real-World Safety of the Pfizer-BioNTech COVID-19 vaccine in the EU Non-Interventional *Planned*	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.	Primary data collection cohort study	EU general population	Final draft protocol submission for EMA review:	31-Jan-2021
					Final CSR submission:	31-Mar-2024

Table 40. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	**Study Title** **Study Type** *Study Status*	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
C4591015 Not available	A Phase 2/3, Placebo-Controlled, Randomized, Observer-Blinded Study to Evaluate the Safety, Tolerability, and Immunogenicity of a SARS-CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older Interventional *Planned*	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women	Randomized, placebo-controlled, observer-blind study	Healthy pregnant women 18 years of age or older vaccinated during their 24 to 34 weeks of gestation	Protocol draft submission: Final CSR submission:	28-Feb-2021 30-Apr-2023
C4591014 US	A non-interventional, test-negative design study to evaluate the effectiveness of Pfizer-BioNTech COVID-19 vaccine (BNT162b2) against acute 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) Non-Interventional (Retrospective database analysis) *Planned*	To determine the effectiveness of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) when administered outside of the clinical setting. To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.	Non-interventional study (test-negative design) of individuals presenting with symptoms of potential COVID-19 illness in a real-world setting	Individuals ≥16 years of age with acute respiratory illness admitted to the emergency department or hospital	Protocol draft submission: Final CSR submission:	31-Mar-2021 30-Jun-2023

Table 40. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type ***Study Status***	Rationale and Study Objectives	Study design	Study populations	Milestones	
WI235284 US	A low-interventional, test-negative design study to evaluate the effectiveness of Pfizer-BioNTech COVID-19 vaccine (BNT162b2) against acute respiratory illness due to SARS-CoV-2 infection among individuals ≥18 years of age in a real-world setting (Atlanta, Georgia, USA). Low-Interventional (Case-control nested in prospective Research Collaboration) *Planned*	To determine the effectiveness of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) when administered outside of the clinical setting. To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.	Low-interventional study (test-negative design) of individuals presenting with symptoms of potential COVID-19 illness in a real-world setting	Individuals ≥18 years of age with acute respiratory illness admitted to the hospital	Protocol draft submission: Final CSR submission:	31-Mar-2021 30-Jun-2023
WI255886 Ex-EU[a]	A non-interventional, test-negative design study to evaluate the effectiveness of Pfizer-BioNTech COVID-19 vaccine (BNT162b2) against acute respiratory illness due to SARS-CoV-2 infection among individuals ≥18 years of age in a real-world setting. Non-Interventional (Case-control nested in prospective Research Collaboration) *Planned*	To determine the effectiveness of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) when administered outside of the clinical setting. To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.	Non-interventional study (test-negative design) of individuals presenting with symptoms of potential COVID-19 illness in a real-world setting	Individuals ≥18 years of age with acute respiratory illness admitted to the hospital	Protocol draft submission: Final CSR submission:	31-Mar-2021 30-Jun-2023

Table 40. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
BNT162-01 Cohort 13 EU	Immunogenicity of COVID-19 mRNA vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses Interventional *Ongoing*	To assess potentially protective immune responses in immunocompromised adults	Dose escalating Open uncontrolled	Use in immunocompromised patients	IA submission: Final CSR submission:	30-Sep-2021 31-Dec-2022
C4591018 US	Phase II study of BNT162b2 in adults receiving immunomodulators for rheumatoid arthritis (RA) Interventional *Planned*	Safety, immunogenicity over 12 months. Description of COVID-19 cases. RA activity by Clinical Disease Activity Index. N-antigen antibodies for detection of asymptomatic infection.	Open uncontrolled	Immunocompromised adults with autoimmune disease (rheumatoid arthritis)	Protocol submission: IA submission:	28-Feb-2021 31-Dec-2021
Safety and immunogenicity in high risk adults US, EU	Phase II study in high risk adults Interventional *Planned*	Safety, immunogenicity over 12 months in frail elderly, immunocompromised, autoimmune and other high-risk individuals. Description of COVID-19 cases. N-antigen antibodies for detection of asymptomatic infection.	Open uncontrolled	High risk adults including frail elderly, those having autoimmune disease, chronic renal disease and immunocompromising conditions	Protocol submission: Final CSR submission:	30-Jun-2021 31-Dec-2022

Table 40. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
ACCESS/VAC4EU EU	A Post-Approval Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the Pfizer-BioNTech COVID-19 vaccine in the EU Non-Interventional *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Secondary database analysis of observational data to estimate incidence rates of safety events of interest and other clinically significant events in cohorts of COVID-19 vaccine recipients in the EU	General population	Protocol submission: Final CSR submission:	28-Feb-2021 31-Jan- 2024
Co-administration study with seasonal influenza vaccine Not available	Co-administration of BNT162b2 with seasonal influenza vaccine Interventional *Planned*	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Not available at this time	General population	Protocol submission: Final CSR submission:	30-Sep-2021 31-Dec-2022

[a]. United Kingdom.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Table 41. On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) Status (*planned/on-going*)	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
Category 2					
C4591001 *Ongoing*	Global	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in patients with co-morbidities (C4591001 subset) Long term safety data.	CSR submission upon regulatory request:	Any time
				CSR submission 6 months post Dose 2:	31-Dec-2021
				Final CSR submission with supplemental follow-up:	31-Aug-2023

Table 41. On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) Status (*planned/on-going*)	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
Category 3					
C4591011 *Planned*	US	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission:	30-Jun-2021
					31-Dec-2021
					30-Jun-2022
					31-Dec-2022
				Final CSR submission:	31-Dec-2023
C4591012 *Planned*	US	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission:	30-Jun-2021
					31-Dec-2021
					30-Jun-2022
					31-Dec-2022
				Final CSR submission:	31-Dec-2023

Table 41. On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) Status (*planned/on-going*)	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
C4591010 *Planned*	EU	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest Use in pregnancy Long-term safety data.	Final draft protocol submission for EMA review:	31-Jan-2021
				Final CSR submission:	31-Mar-2024
C4591015 *Planned*	Not available	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women	Use in pregnancy and while breast feeding.	Protocol draft submission:	28-Feb-2021
				Final CSR submission:	30-Apr-2023
C4591014 *Planned*	US	To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Protocol draft submission:	31-Mar-2021
				Final CSR submission:	30-Jun-2023
WI235284 *Planned*	US	To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Protocol draft submission:	31-Mar-2021
				Final CSR submission:	30-Jun-2023
WI255886 *Planned*	Ex-EU[a]	To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Protocol draft submission:	31-Mar-2021
				Final CSR submission:	30-Jun-2023

Table 41. On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) **Status (*planned/on-going*)**	**Country**	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
BNT162-01 Cohort 13 *Ongoing*	EU	To assess potentially protective immune responses in immunocompromised adults	Use in immunocompromised patients.	IA submission: Final CSR submission:	30-Sep-2021 31-Dec-2022
C4591018 *Planned*	US	Safety, immunogenicity over 12 months. Description of COVID-19 cases. RA activity by Clinical Disease Activity Index. N-antigen antibodies for detection of asymptomatic infection.	Use in immunocompromised patients Use in patient with autoimmune or inflammatory disorders.	Protocol submission: IA submission:	28-Feb-2021 31-Dec-2021
Safety and immunogenicity in high risk adults *Planned*	EU, US	Safety, immunogenicity over 12 months in frail elderly, immunocompromised, autoimmune and other high-risk individuals. Description of COVID-19 cases. N-antigen antibodies for detection of asymptomatic infection.	Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders).	Protocol submission: Final CSR submission:	30-Jun-2021 31-Dec-2022
ACCESS/VAC4EU *Planned*	EU	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long term safety data.	Protocol submission: Final CSR submission:	28-Feb-2021 31-Jan-2024

Table 41. On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) **Status (*planned/on-going*)**	**Country**	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
Co-administration study with seasonal influenza vaccine *Planned*	Not available	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines.	Protocol submission:	30-Sep-2021
				Final CSR submission:	31-Dec-2022

a. United Kingdom.

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

None.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

The product information is sufficient to mitigate the current identified and potential risks of COVID-19 mRNA vaccine. The necessary information to ensure appropriate use of the product is included in the relevant sections of the SmPC. No additional measures for risk minimisation are considered necessary by the MAA at this time. The proposed minimisation measures are summarised in the table below for each safety concern.

Table 42. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Important Identified Risk	
Anaphylaxis	Routine risk communication: SmPC section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Important Potential Risk	
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Missing Information	
Use in pregnancy and while breast feeding	Routine risk communication: SmPC section 4.6 Fertility, pregnancy and lactation PL section 2. What you need to know before you receive Comirnaty Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

Table 42. Description of Routine Risk Minimisation Measures by Safety Concern

Use in immunocompromised patients	Routine risk communication: SmPC section 4.4 Special warnings and precautions for use and section 5.1 Pharmacodynamic properties. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk communication: SmPC section 5.1 Pharmacodynamic properties. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in patients with autoimmune or inflammatory disorders	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Interaction with other vaccines	Routine risk communication: SmPC section 4.5 Interaction with other medicinal products and other forms of interaction Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Long term safety data	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Table 43. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Anaphylaxis	Routine risk minimisation measures: SmPC sections 4.4. and 4.8. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about potential anaphylactic reactions in individuals who have received the COVID-19 mRNA vaccine (cross. Ref with Section III.1). Additional pharmacovigilance activities: Studies (Final CSR Due Date): • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is 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 (cross. Ref with Section III.1). Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591001 (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).

Table 43. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnancy and while breast feeding	Routine risk minimisation measures: SmPC section 4.6; PL section 2. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591010 [a](31-Mar-2024) • C4591011 [a] (31-Dec-2023) • C4591015 (30-Apr-2023) • ACCESS/VAC4EU [a] (31-Jan-2024).
Use in immunocompromised patients	Routine risk minimisation measures: SmPC sections 4.4 and 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR or IA Due Date) • BNT162-01 Cohort 13 (IA: 30-Sep-2021, CSR: 31-Dec-2022) • C4591018 (IA: 31-Dec-2021) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: SmPC section 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date submission) • C4591001 subset (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024) • Safety and immunogenicity in high risk adults (31-Dec-2022).
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591018 (31-Dec-2021) • ACCESS/VAC4EU (31-Jan-2024).

Table 43. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Interaction with other vaccines	Routine risk minimisation measures: SmPC section 4.5. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • Co-administration study with seasonal influenza vaccine (31-Dec-2022).
Long term safety data	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date or IA CSR submission) • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).

a. Please note that studies C4591010, C4591011 and ACCESS/VAC4EU address only “Use in pregnancy”.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Comirnaty.

This is a summary of the risk management plan (RMP) for Comirnaty. The RMP details important risks of Comirnaty, how these risks can be minimised, and how more information will be obtained about Comirnaty's risks and uncertainties (missing information).

Comirnaty's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Comirnaty should be used.

This summary of the RMP for Comirnaty should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Comirnaty's RMP.

I. The Medicine and What It Is Used For

Comirnaty is a vaccine for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older. (see SmPC for the full indication). It contains nucleoside-modified messenger RNA formulated in lipid nanoparticles as the active substance and it is given intramuscularly.

Further information about the evaluation of Comirnaty's benefits can be found in Comirnaty's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage www.ema.europa.eu/en/medicines/human/EPAR/comirnaty .

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Comirnaty, together with measures to minimise such risks and the proposed studies for learning more about Comirnaty's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Comirnaty is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Comirnaty are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Comirnaty. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 44. List of Important Risks and Missing Information

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 while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference.

Table 45. Important Identified Risk: Anaphylaxis

Evidence for linking the risk to the medicine	Events of anaphylaxis have been reported.
Risk factors and risk groups	Known allergy to the vaccine or its ingredients.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4. and 4.8. Additional risk minimisation measures: None.

Table 45. Important Identified Risk: Anaphylaxis

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C4591001 • C4591010 • C4591011 • C4591012 • ACCESS/VAC4EU See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 46. Important Potential Risk: Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)

Evidence for linking the risk to the medicine	VAED is considered a potential risk because it has not been seen in human studies with this or other COVID-19 vaccines being studied. It has not been seen in vaccine studies in animal models of the SARS-CoV-2 virus either. However, in selected vaccine studies in animal models as well as in some laboratory studies in animal cells infected with 2 other related coronaviruses (SARS-CoV-1 and MERS-CoV), abnormalities in immune responses or cellular responses indicative of VAED were observed. Because of this, VAED is considered a potential risk. In the past there have been other examples of particularly respiratory viruses where VAED has been observed. For example, some children who received an inactivated respiratory syncytial virus vaccine (a different type of virus), had worse signs of disease when they were subsequently infected with respiratory syncytial virus. VAED is thought to occur by several mechanisms where the immune response is not fully protective and actually either causes the body to have an inflammatory reaction due to the type of immune response with specific types of T-cells, or the body does not produce enough strong antibodies to prevent SARS-CoV-2 infection of cells or produces weak antibodies that actually bind to the virus and help it to enter cells more easily, leading to worse signs of disease.
Risk factors and risk groups	It is thought that the potential risk of VAED may be increased in individuals producing a weak antibody response or in individuals with decreasing immunity over time.
Risk minimisation measures	Routine risk minimisation measures None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C4591001 • C4591011 • C4591012 • ACCESS/VAC4EU See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 47. Missing Information: Use in pregnancy and while breast feeding

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6; PL section 2. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C4591010 [a] • C4591011 [a] • C4591015 • ACCESS/VAC4EU See Section II.C of this summary for an overview of the post-authorisation development plan.

a. Please note that studies C4591010, C4591011 and ACCESS/VAC4EU address only "Use in pregnancy".

Table 48. Missing Information: Use in immunocompromised patients

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 5.1. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • BNT162-01 cohort 13 • C4591018 • C4591011 • C4501012 • ACCESS/VAC4EU. See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 49. Missing Information: Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Risk minimisation measures	Routine risk minimisation measures: SmPC section 5.1. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C4591001 subset • C4591011 • C4501012 • ACCESS/VAC4EU • Safety and immunogenicity in high risk adults See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 50. Missing Information: Use in patients with autoimmune or inflammatory disorders

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C4591011 • C4501012 • ACCESS/VAC4EU • C4591018 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 51. Missing Information: Interaction with other vaccines

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.5. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Co-administration study with seasonal influenza vaccine See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 52. Missing Information: Long term safety data

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C4591001 • C4591010 • C4591011 • C4591012 • ACCESS/VAC4EU See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

Study	Purpose of the study
C4591001	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine. An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study	Purpose of the study
C4591011	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.
C4591012	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.
C4591010	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.
C4591015	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine. Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women.
C4591014	To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.
WI235284	To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.
WI255886	To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.
BNT162-01 Cohort 13	To assess potentially protective immune responses in immunocompromised adults.
C4591018	Safety, immunogenicity over 12 months; description of COVID-19 cases; rheumatoid arthritis activity by Clinical Disease Activity Index; N-antigen antibodies for detection of asymptomatic infection.
Safety and immunogenicity in high risk adults	Safety, immunogenicity over 12 months in frail elderly, immunocompromised, autoimmune and other high-risk individuals; description of COVID-19 cases; N-antigen antibodies for detection of asymptomatic infection.

Study	Purpose of the study
ACCESS/ VAC4EU	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.
Co-administration study with seasonal influenza vaccine	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Table of contents

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Instructions for use:

This Data Capture Aid (DCA) is intended to capture the available clinical details about the nature and severity of COVID-19 illness experienced, particularly in relation to potential cases of vaccine lack of effect or vaccine associated enhanced disease (VAED).

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____
Suspect product: _____
Reported event term prompting special follow-up activities: _____
AE onset date (dd-Mmm-yyyy): _____
Patient Age (e.g., 65 years): _____

Patient Gender: ☐ Male ☐ Female ☐ Not Stated

Race: ☐ White ☐ Black or African American ☐ Native American ☐ Alaska Native ☐ Native Hawaiian ☐ Asian ☐ Other ☐ Refused or Don't Know

Ethnic Group: ☐ Hispanic/LatinX ☐ Non-Hispanic/Non-LatinX

Reporter Information

Name of reporter completing this form *(If other than addressee, provide contact information below):*		
Phone Number:	Fax Number:	Email Address:

1. Product information (Pfizer-BioNTech COVID-19 Vaccine)

Dose	Date (dd-Mmm-yyyy)	Site of injection	Route	Batch/Lot number
1st dose				
2nd dose				

Follow-up Questions

Please provide additional details on a separate page if needed and reference the question number.

1. Does the patient have a positive test for SARS-CoV2?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (and indicate if this is a new infection or a recurrence)*
Details: (Please specify date of test and type of test – e.g., nasal swab reverse transcription–polymerase chain reaction (RT-PCR) test or nucleic acid amplification–based test (NAAT) or antigen test)

2. Does the patient have SARS-CoV2 antibodies at diagnosis?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details: (Please specify date of test, whether IgM /IgG or both and the titer if available)

3. Was/Is the patient hospitalized?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., duration of hospitalization)*
Details:

4. Was/Is the patient admitted to an Intensive Care Unit?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., duration of hospitalization)*
Details:

5. Is the patient still hospitalized?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., duration of hospitalization)*
Details:

6. If discharged, did the patient have SARS-CoV2 antibodies at hospital discharge?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details: (Please specify date of test, whether IgM /IgG or both and the titer if available)

7. Did the patient display clinical signs at rest indicative of severe systemic illness?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., Fever, RR ≥30 breaths per minute, HR ≥125 beats per minute, use of vasopressors to maintain BP, SpO2 ≤93% on room air, PaO2/FiO2 <300 mm Hg)?)*
Details:

8. Did the patient require supplemental oxygen (including high flow or ECMO) or receive mechanical ventilation?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., oxygen requirements, pulse oximetry results)*
Details:

9. Please provide information on any new or worsened symptoms/signs during the COVID-19 illness experienced (including date of onset/worsening)

Multiorgan failure ☐ Unknown ☐ No ☐ Yes → *If Yes, please indicate which organ systems were affected and provide information on the applicable systems below*

☐ Respiratory ☐ Cardiovascular ☐ Gastrointestinal/Hepatic ☐ Vascular ☐ Renal ☐ Neurological ☐ Hematological ☐ Dermatological ☐ Other

Respiratory ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Dyspnea** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Tachypnea** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Hypoxemia** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **COVID-pneumonia** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Respiratory failure** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Acute Respiratory Distress Syndrome (ARDS)** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Other** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

Cardiovascular ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Heart failure** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Cardiogenic shock** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Acute myocardial infarction** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Arrhythmia** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Myocarditis** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Other** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

Gastrointestinal/Hepatic ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Vomiting** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Diarrhea** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Abdominal pain** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Jaundice** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Acute liver failure** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Other** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

Vascular ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Deep vein thrombosis** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Pulmonary embolism** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Limb ischemia** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Vasculitis** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Other (in particular any other thromboembolic events)** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

Renal ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Acute kidney injury** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Renal failure** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Other** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

Neurological ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Altered consciousness** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Convulsions/seizures ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Encephalopathy ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Meningitis ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Cerebrovascular accident ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details and indicate if ischemic or hemorrhagic*
Other ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

Hematological ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Thrombocytopenia ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (see also Q14)*
Disseminated intravascular coagulation ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (see also Q14)*
Other ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

Dermatological ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Chillblains ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Erythema multiforme ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Other ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

OTHER (e.g. multisystem inflammatory syndrome [MIS]) ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

10. Did the patient receive any additional therapies for COVID-19?

Therapy	Date Started (dd-Mmm-yyyy)	Date Stopped (dd-Mmm-yyyy)	Dose/Any additional information
☐ Remdesivir			
☐ Hydroxychloroquine/chloroquine			
☐ Azithromycin			
☐ Corticosteroids			
☐ Other (Please Specify)			

11. Did the event require the initiation of new medication or other treatment or procedure?
☐ Unknown ☐ No ☐ Yes → If Yes, please provide details
Details:

12. Patient's outcome with COVID-19:

☐ Recovering ☐ Recovered ☐ Not recovered ☐ Unknown ☐ Fatal, Date (dd-Mmm-yyyy): ……

If outcome is fatal, was an autopsy performed? ☐ Unknown ☐ No ☐ Yes → *If Yes, please* provide autopsy findings

Details:

13. How many days from the SARS-CoV2 diagnosis did it take before the SARS-CoV2 antigen test became negative?

14. Were any of the following laboratory tests or diagnostic studies performed? *Please specify laboratory data with units, date of test, and reference ranges; and please provide printouts and photographs if available:*

Laboratory Test or Diagnostic Studies	Date Performed (dd-Mmm-yyyy)	Results with units, if applicable	Reference Ranges, if applicable (or please state if abnormal or elevated/reduced)
☐ Test for SARS-CoV-2 by PCR, or other commercial or public health assay			
☐ Imaging for COVID-Pneumonia (e.g.CXR, CT)			
☐ Other radiological investigations (e.g. MRI, angiogram, V/Q scan)			
☐ Imaging for thrombo-embolic events (e.g. doppler or CT)			
☐ Hematology (e.g. leucocyte count [including neutrophil and lymphocyte counts], hemoglobin, platelet count, coagulation parameters [PT, PTT, D-Dimer, INR], fibrinogen, B and T cell function assays)			
☐ Clinical chemistry (e.g. serum creatinine, glomerular filtration rate [GFR], liver enzymes, bilirubin, albumin, B-type natriuretic peptide [BNP], troponin)			
☐ Inflammatory markers (e.g. CRP, ESR, procalcitonin, ferritin, LDH, cytokines [including IL-6])			
☐ Urinalysis			
☐ Evidence of hypoxemia (e.g. PaO_2/FiO_2 [P/F ratio], SpO_2/FiO_2 [S/F ratio]), hypercapnia ($PaCO_2$) or acidosis (pH)			
☐ Other relevant tests (please specify):_____			

Past Medical History Questions

Please provide additional details on a separate page if needed and reference the question number.

15. Does the patient have a history of any of the following?

☐ Hypertension
☐ Diabetes
☐ Heart Disease *(please specify)*
☐ Lung Disease *(please specify)*
☐ Liver disease *(please specify)*
☐ Kidney disease *(please specify)*
☐ Cancer *(please specify)*
☐ Immunosuppressive disorder *(please specify)*
☐ Obesity
☐ Other *(please specify)*

Details:

16. Is the patient a smoker/former smoker?

☐ Current Smoker ☐ Former smoker ☐ No

Details:

17. Was the patient taking any medications routinely prior to the event being reported?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

18. Have any pre-existing diseases worsened during the SARS-CoV2 infection (please specify)

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

19. Has the patient been treated with immunomodulating or immunosuppressing medications or received any other vaccines around the time of COVID-19 vaccination?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

Revision History

Revision	Effective Date	Summary of Revisions
1.0	07-Dec-2020	New DCA