COMIRNATY (COVID-19 mRNA VACCINE)
RISK MANAGEMENT PLAN

RMP Version number: 2.3

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)
	18 June 2021 (Pfizer Safety Database)
16 years and older	13 March 2021 (Pfizer Clinical Database)
	23 October 2020 (BioNTech Clinical Database)
	28 February 2021 (Pfizer Safety Database and Post-Authorisation Exposure)
	18 June 2021 (Pfizer Safety Database)
myocarditis/pericarditis	18 June 2021 (Pfizer Safety Database)

Date of final sign off: 24 September 2021

Rationale for submitting an updated RMP (vs 2.2):
This Type II variation includes an updated Comirnaty EU RMP that merges versions 2.0 and 2.1, as per PRAC/CHMP preliminary assessment report/Request for Supplementary Information (Procedure No. EMEA/H/C/005735/II/0036) recommendation. This RMP v 2.2 received positive Opinion on 16 September 2021 and EC decision on 23 September 2021.

Rationale for submitting an updated RMP (v 2.3): This Type II variation includes the new important identified risk of myocarditis and pericarditis based on the Signal of Myocarditis, pericarditis for COVID-19 mRNA vaccine (nucleoside-modified) - COMIRNATY (EPITT ref. No. 19712) - EMA/PRAC/355882/2021 recommendation dated 08 July 2021.

Following receipt of the PRAC Rapporteur's preliminary assessment report and the Request for Supplementary Information with regard to the RMP v 2.3 submitted in August 2021, this updated draft includes information on C4591038 (former C4591021 substudy), as requested.

Summary of significant changes in this RMP:

RMP Part/Module	Major Change (s)	
	RMP v 2.2	**RMP v 2.3**
PART I PRODUCT(S) OVERVIEW	Change to align the age indication.	No changes made.
PART II SAFETY SPECIFICATION		
PART II.Module SI Epidemiology of the Indication(s) and Target Populations	Change to align the age indication.	No changes made.
PART II.Module SII Non-Clinical Part of the Safety Specification	No changes made.	No changes made.
PART II.Module SIII Clinical Trial Exposure	Text and exposure tables consolidated.	No changes made.
PART II.Module SIV Populations Not Studied in Clinical Trials	Text in SIV.1 and SIV.3 and Table 33 consolidated.	No changes made.
PART II.Module SV Post-Authorisation Experience	No changes made.	Exposure data updated at DLP 18 June 2021
PART II.Module SVI Additional EU Requirements for the Safety Specification	No changes made.	No changes made.
PART II.Module SVII Identified and Potential Risks	Consolidated data in Table 39 (Anaphylaxis) and Table 41 (VAED/VAERD).	Addition of data related to the new important identified risk of myocarditis/pericarditis Data from the safety database as of 18 June 2021, for anaphylaxis and VAED/VAERD updated
PART II.Module SVIII Summary of the Safety Concerns	No changes made.	Addition of important identified risk myocarditis/pericarditis
PART III PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)		
III.1 Routine Pharmacovigilance activities III.2 Additional Pharmacovigilance Activities and III.3 Summary Table of Additional Pharmacovigilance Activities	No changes made.	Addition of data related to the new important identified risk of myocarditis/pericarditis Planned/ongoing Post-authorization safety studies (protocols C4591011 [US], C4591012 [US], and C4591021 [EU], the new C4591038 (former C4591021 sub-study) [EU] and inclusion of two new US PASS: C4591009 and study C4591036 (former Pediatric Heart Network)
PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES	No changes made.	No changes made.

RMP Part/Module	Major Change (s)	
	RMP v 2.2	**RMP v 2.3**
PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)		
V.1 Routine Risk Minimisation Measures V.2 Additional Risk Minimisation Measures V.3 Summary of Risk Minimisation Measures	No changes made.	Addition of data related to the new important identified risk of myocarditis/pericarditis Changes to align to the updated version of the EU SmPC DHCP as additional RMM
PART VI SUMMARY OF THE RISK MANAGEMENT PLAN		
I The Medicine and What It Is Used For II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks	Change to align the age indication.	Addition of data related to the new important identified risk of myocarditis/pericarditis
PART VII ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 8: Changes to reflect the consolidated information.	Annexes 2, 3, 6 and 8 updated

Other RMP versions under evaluation:

RMP version number: 2.4

Submitted on: 21 September 2021

Procedure number: EMEA/H/C/005735/II/0036

Details of the currently approved RMP

Version number: 2.2

Approved with procedure: EMEA/H/C/005735/II/0036

Date of approval (EC date): 23 September 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
ACIP	Advisory Committee on Immunisation Practices
AE	adverse event
AESI	Adverse event of special interest
A:G	albumin:globulin
ARDS	acute respiratory distress syndrome
BALB/c	bagg albino
BC	Brighton Colloboration
BMI	body mass index
BP	blood pressure
CD4, CD8	cluster of differentiation-4,8
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CLL	chronic lymphocytic leukaemia
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
DHPC	Direct Healthcare Professional Communication
DLP	data-lock point
DoD	Department of Defense
ECDC	European Center for Disease Control
ED	emergency department
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

Abbreviation	Definition of Term
IND	investigational new drug
LNP	lipid nanoparticle
MAA	marketing authorisation applicant
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MERS-CoV	Middle East respiratory syndrome-coronavirus
MHS	Military Health System
MIS-C	multisystem inflammatory syndrome in children
NDA	new drug application
NHP	nonhuman primate
NICE	National Institute for Health and Care Excellence
NSCLC	non-small-cell lung carcinoma
OCS	oral corticosteroids
PC	product complaint
PK	pharmacokinetic
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
TNF	tumour necrosis factor
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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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)	J07BX03
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 for dispersion for injection (sterile concentrate). 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 MAA 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/	Active Cases[a]	Prevalence: Active Cases/	Total Deaths	Mortality: Deaths / 100,000	Population
Global	115,760,943	1,485	21,707,680	278	2,571,518	33	7,794,824,793
EU-27	22,642,536	5,083	6,113,464	1,462	553,363	124	445,424,167
UK	4,194,785	6,157	1,065,282	1,564	123,783	182	68,125,249
EU-27 + UK	26,837,321	5,226	7,178,746	1,398	677,146	132	513,549,416
US	29,456,377	8,864	8,921,400	2,685	531,652	160	332,304,437
EU-27 Countries							
Austria	465,322	5,147	21,028	233	8,625	95	9,040,866
Belgium	774,344	6,662	699,566	6,019	22,141	191	11,623,476
Bulgaria	253,183	3,662	33,770	488	10,413	151	6,913,156
Croatia	244,205	5,973	3,322	81	5,555	136	4,088,197
Cyprus	35,620	2,936	33,331	2,747	232	19	1,213,250
Czech Republic	1,269,058	11,836	154,580	1,442	20,941	195	10,722,330
Denmark	212,798	3,665	6,995	120	2,370	41	5,805,897
Estonia	69,193	5,214	17,938	1,352	615	46	1,327,135
Finland	59,442	1,072	12,683	229	759	14	5,546,504
France	3,810,316	5,829	3,461,485	5,295	87,542	134	65,370,546
Germany	2,472,896	2,945	126,785	151	71,711	85	83,963,843
Greece	197,279	1,899	21,157	204	6,597	64	10,388,744
Hungary	439,900	4,561	98,361	1,020	15,324	159	9,643,837
Ireland	221,189	4,446	193,468	3,889	4,357	88	4,974,683
Italy	2,976,274	4,927	437,421	724	98,635	163	60,401,999
Latvia	88,022	4,702	9,233	493	1,654	88	1,872,109
Lithuania	200,349	7,430	10,859	403	3,281	122	2,696,596
Luxembourg	55,902	8,834	3,074	486	643	102	632,773
Malta	23,226	5,251	3,000	678	321	73	442,333
Netherlands	1,101,430	6,418	-	-	15,697	92	17,160,343
Poland	1,735,406	4,589	249,567	660	44,360	117	37,818,722
Portugal	806,626	7,926	64,797	637	16,430	161	10,176,690
Romania	812,318	4,242	44,953	235	20,586	108	19,151,141
Slovakia	314,359	5,756	51,570	944	7,489	137	5,461,420
Slovenia	192,266	9,247	10,751	517	3,874	186	2,079,130
Spain	3,136,321	6,706	343,770	735	70,247	150	46,766,954
Sweden	675,292	6,659	-	-	12,964	128	10,141,493

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

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

People who carry the virus but remain asymptomatic are less likely to be tested and therefore mild cases are likely underreported. The numbers should therefore be interpreted with caution.[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).

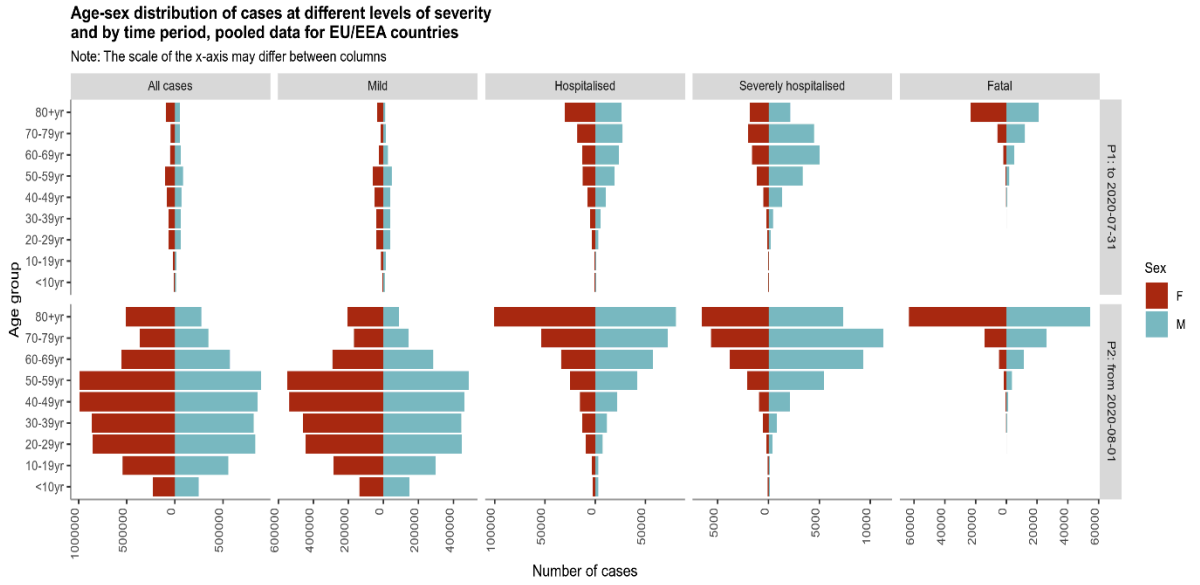
In the US, the prevalence on 03 March 2021 was nearly twice as high as the combined EU + UK estimates, with 2,685 active cases per 100,000.[4] The prevalence in the US was 653 per 100,000 on 28 July 2020.[5]

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 hospitalized or a case that resulted in death.

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

Event	Age Group	Age %	Sex	Sex %	Race[b]	Race %	Age x Sex %		
							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]

Event	Age Group	Age %	Sex	Sex %	Race[b]	Race %	Age x Sex %		
							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]

Characteristic	Category	COVID-19 death Hazard Ratio	
		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]

Characteristic	Category	COVID-19 death Hazard Ratio	
		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 authorized in the EU 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]

Sign/Symptom	No. (%) with sign/symptom	
	Pediatric	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.[11,14,49] 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.[50]

COVID-19 symptoms can persist weeks or months beyond the acute infection.[51,52] 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).[53]

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%).[54] 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.[33,55,56]

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 (COVID-19 mRNA vaccine) included pharmacology (mouse immunogenicity and NHP immunogenicity and challenge studies), pharmacokinetic (series of biodistribution, metabolism and pharmacokinetic studies), and toxicity (2 GLP rat repeat-dose toxicity) studies in vitro and in vivo. A GLP DART study has been completed. No additional toxicity studies are planned for COVID-19 mRNA vaccine.

Nonclinical studies in mice and NHP for 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.[57] Rhesus macaques (Study VR-VRT-10671) that had received two IM immunisations with 100 µg COVID-19 mRNA vaccine 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.[58] COVID-19 mRNA vaccine provided complete protection from the presence of detectable viral RNA in the lungs compared to the saline control with no clinical, radiological or histopathological evidence of vaccine-elicited disease enhancement.

An intravenous rat PK study, using an LNP with the identical lipid composition as 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.[59]

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[60] 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.[61] 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.

Administration of COVID-19 mRNA vaccine to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg) was associated with non-adverse effects (body weight, food consumption and effects localized to the injection site) after each dose administration. However, there were no effects of COVID-19 mRNA vaccine administration on mating performance, fertility, or any ovarian or uterine parameters in the F0 female rats nor on embryo-fetal or postnatal survival, growth, or development in the F1 offspring. An immune response was confirmed in F0 female rats following administration of each vaccine candidate and these responses were also detectable in the F1 offspring (fetuses and pups).

In summary, the nonclinical safety findings related to 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]	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[60], 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 • No vaccine-related effects on female fertility or the development of fetuses or offspring were observed in a DART study of COVID-19 mRNA vaccine 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.[59] In addition, the components of the vaccine construct are lipids and RNA and are not expected to have carcinogenic or genotoxic potential.

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 vaccine 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 56- to 85-year age cohort.

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

- the reactogenicity profile for BNT162b2 was more 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 BNT162b2 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 9, Table 11, Table 17, Table 19, Table 21, and Table 23) 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 approximately 46,000 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, MAA 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 are 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.

Analysis of 6-month post Dose-2 data was conducted on 16 years of age and older cohort reported at 13 March 2021.

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.

At the cut-off date of 13 March 2021, a total of 46,505 participants (23,332 received COVID-19 mRNA vaccine and 23,173 placebo) were vaccinated in the COVID-19 mRNA vaccine clinical development program.

Participants aged 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, at the cut-off date of 13 March 2021, is shown in Table 9, Table 11, Table 17, Table 21, and Table 23.

Participants 16 years of age and older

At the cut-off date of 13 March 2021, a total of 44,245 participants were vaccinated in the COVID-19 mRNA vaccine clinical development program:

- 21,745 participants received 2 doses and 360 received 1 dose of COVID-19 mRNA vaccine during blinded follow-up period; 96 participants from study BNT162-01 received 2 doses of the vaccine.

- 22,044 participants received placebo (of these 19,647 then received 1 dose of COVID-19 mRNA vaccine in the open-label follow-up period after unblinding); 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 28.

In addition, exposure in clinical studies in special populations is provided in Table 29, Table 30, Table 31, Table 32 and in Table 33.

Table 9. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Blinded Placebo-Controlled Follow-up Period

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

Table 9. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg		
1 Dose	17	17
2 Doses	3624	7248
Total	3641	7265
≥75 years to ≤84 years		
Vaccine 20 µg		
2 Doses	3	6
Total	3	6
Vaccine 30 µg		
1 Dose	3	3
2 Doses	899	1798
Total	902	1801
≥85 years		
Vaccine 30 µg		
1 Dose	2	2
2 Doses	21	42
Total	23	44

Note: 30 µg includes data from phase 1 and phase 2/3.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:42) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s912

Table 10. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

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

Table 10. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
>55 years to ≤64 years		
Vaccine 30 µg		
1 Dose	17	17
≥65 years to ≤74 years		
Vaccine 30 µg		
1 Dose	8	8
≥75 years to ≤84 years		
Vaccine 30 µg		
1 Dose	1	1
≥85 years		
Vaccine 30 µg		
1 Dose	2	2

Note: 30 µg includes data from phase 1 and phase 2/3.
Note: Subjects who received 2nd Dose of BNT162b2 after unblinding.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s9123

Table 11. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥12 years to ≤15 years[a]		
Vaccine 30 µg		
1 Dose	30	30
2 Doses	19	38
Total	49	68
≥16 years to ≤17 years		
Vaccine 30 µg		
1 Dose	107	107
2 Doses	186	372
Total	293	479

Table 11. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥18 years to ≤55 years		
Vaccine 30 µg		
1 Dose	2713	2713
2 Doses	8419	16838
Total	11132	19551
>55 years to ≤64 years		
Vaccine 30 µg		
1 Dose	655	655
2 Doses	3330	6660
Total	3985	7315
≥65 years to ≤74 years		
Vaccine 30 µg		
1 Dose	128	128
2 Doses	3286	6572
Total	3414	6700
≥75 years to ≤84 years		
Vaccine 30 µg		
1 Dose	23	23
2 Doses	783	1566
Total	806	1589
≥85 years		
Vaccine 30 µg		
1 Dose	1	1
2 Doses	16	32
Total	17	33

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: 27MAR2021 (12:46)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s9122

Table 12. Exposure to BNT162b2 by Age Group and Dose (BNT162-01)

Age Group Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
≥18 years to ≤64 years		
Vaccine 1 µg		
1 Dose	1	1
2 Doses	11	22
Total	12	23
Vaccine 3 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24
Vaccine 10 µg		
1 Dose	1	1
2 Doses	17	34
Total	18	35
Vaccine 20 µg		
1 Dose	0	0
2 Doses	17	34
Total	17	34
Vaccine 30 µg		
1 Dose	0	0
2 Doses	18	36
Total	18	36
≥65 years to ≤74 years		
Vaccine 1 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 3 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 10 µg		
1 Dose	0	0
2 Doses	5	10
Total	5	10

Table 12. 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	6	12
Total	6	12
Vaccine 30 µg		
1 Dose	0	0
2 Doses	6	12
Total	6	12
≥75 years to ≤84 years		
Vaccine 1 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 3 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 10 µg		
1 Dose	0	0
2 Doses	1	2
Total	1	2
Vaccine 20 µg		
1 Dose	0	0
2 Doses	1	2
Total	1	2
Vaccine 30 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0

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

Table 13. Exposure to BNT162b2 by Dose (Totals) (C4591001) – Blinded Placebo-Controlled Follow-up Period

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

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

Table 14. Exposure to BNT162b2 by Dose (Totals) (C4591001) – Open-Label Follow-up Period –Subjects Who Originally Received BNT162b2

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

Note: 30 µg includes data from phase 1 and phase 2/3.
Note: Subjects who received 2nd Dose of BNT162b2 after unblinding.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s9223

Table 15. Exposure to BNT162b2 by Dose (Totals) (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

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

Note: 30 µg includes data from phase 1 and phase 2/3.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s9222

Table 16. Exposure to BNT162b2 by Dose (Totals) (BNT162-01)

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

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

Table 17. Exposure to BNT162b2 by Dose, Age Group, and Gender (C4591001) – Blinded Placebo-Controlled Follow-up Period

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

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

Table 18. Exposure to BNT162b2 by Dose, Age Group, and Gender (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

Dose / Age Group	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses	
	Male	Female	Male	Female
Vaccine 30 µg				
≥16 years to ≤17 years	0	3	0	3
≥18 years to ≤55 years	24	34	24	34
>55 years to ≤64 years	12	5	12	5
≥65 years to ≤74 years	4	4	4	4
≥75 years to ≤84 years	0	1	0	1
≥85 years	1	1	1	1
Total	41	48	41	48

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

Table 19. Exposure to BNT162b2 by Dose, Age Group, and Gender (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

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

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

Table 20. 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 ≤64 years	7	5	14	9
≥65 years to ≤74 years	0	0	0	0
≥75 years to ≤84 years	0	0	0	0
Total	7	5	14	9
Vaccine 3 µg				
≥18 years to ≤64 years	5	7	10	14
≥65 years to ≤74 years	0	0	0	0
≥75 years to ≤84 years	0	0	0	0
Total	5	7	10	14
Vaccine 10 µg				
≥18 years to ≤64 years	8	10	16	19
≥65 years to ≤74 years	3	2	6	4
≥75 years to ≤84 years	1	0	2	0
Total	12	12	24	23
Vaccine 20 µg				
≥18 years to ≤64 years	7	10	14	20
≥65 years to ≤74 years	1	5	2	10
≥75 years to ≤84 years	0	1	0	2
Total	8	16	16	32
Vaccine 30 µg				
≥18 years to ≤64 years	10	8	20	16
≥65 years to ≤74 years	2	4	4	8
≥75 years to ≤84 years	0	0	0	0
Total	12	12	24	24

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

Table 21. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

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

Table 21. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥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
Vaccine 20 µg		
Racial origin		
White	10	20
Black or African American	2	4
Total	12	24
Ethnic origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	11	22
Total	12	24
Vaccine 30 µg		
Racial origin		
White	9923	19637
Black or African American	1400	2764
Asian	683	1358
American Indian or Alaska Native	161	311
Native Hawaiian or other Pacific Islander	40	80
Multiracial	427	851
Not reported	71	142
Total	12705	25143
Ethnic origin		
Hispanic/Latino	4000	7874
Non-Hispanic/non-Latino	8650	17160
Not reported	55	109
Total	12705	25143

Table 21. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
>55 years to ≤64 years		
Vaccine 30 µg		
Racial origin		
White	3719	7388
Black or African American	430	849
Asian	135	267
American Indian or Alaska Native	30	58
Native Hawaiian or other Pacific Islander	8	15
Multiracial	76	152
Not reported	10	20
Total	4408	8749
Ethnic origin		
Hispanic/Latino	965	1903
Non-Hispanic/non-Latino	3413	6786
Not reported	30	60
Total	4408	8749
≥65 years to ≤74 years		
Vaccine 10 µg		
Racial origin		
White	12	24
Total	12	24
Ethnic origin		
Non-Hispanic/non-Latino	12	24
Total	12	24
Vaccine 20 µg		
Racial origin		
White	9	18
Total	9	18
Ethnic origin		
Non-Hispanic/non-Latino	9	18
Total	9	18

Table 21. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg		
Racial origin		
White	3272	6528
Black or African American	219	437
Asian	82	164
American Indian or Alaska Native	22	44
Native Hawaiian or other Pacific Islander	6	12
Multiracial	30	60
Not reported	10	20
Total	3641	7265
Ethnic origin		
Hispanic/Latino	583	1158
Non-Hispanic/non-Latino	3038	6067
Not reported	20	40
Total	3641	7265
≥75 years to ≤84 years		
Vaccine 20 µg		
Racial origin		
White	3	6
Total	3	6
Ethnic origin		
Non-Hispanic/non-Latino	3	6
Total	3	6
Vaccine 30 µg		
Racial origin		
White	838	1673
Black or African American	22	44
Asian	31	62
American Indian or Alaska Native	3	6
Native Hawaiian or other Pacific Islander	1	2
Multiracial	7	14
Total	902	1801
Ethnic origin		
Hispanic/Latino	107	213
Non-Hispanic/non-Latino	789	1576
Not reported	6	12
Total	902	1801

Table 21. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥85 years		
Vaccine 30 µg		
Racial origin		
White	20	38
Asian	1	2
American Indian or Alaska Native	1	2
Multiracial	1	2
Total	23	44
Ethnic origin		
Hispanic/Latino	2	4
Non-Hispanic/non-Latino	21	40
Total	23	44

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

Table 22. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥16 years to ≤17 years		
Vaccine 30 µg		
Racial origin		
White	3	3
Total	3	3
Ethnic origin		
Non-Hispanic/non-Latino	3	3
Total	3	3

Table 22. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

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

Table 22. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2

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

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

Table 23. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥12 years to ≤15 years[a]		
Vaccine 30 µg		
Racial origin		
White	45	62
Asian	3	5
Multiracial	1	1
Total	49	68
Ethnic origin		
Hispanic/Latino	2	4
Non-Hispanic/non-Latino	47	64
Total	49	68
≥16 years to ≤17 years		
Vaccine 30 µg		
Racial origin		
White	251	410
Black or African American	11	19
Asian	14	25
American Indian or Alaska Native	2	4
Native Hawaiian or other Pacific Islander	1	2
Multiracial	12	16
Not reported	2	3
Total	293	479
Ethnic origin		
Hispanic/Latino	26	43
Non-Hispanic/non-Latino	266	434
Not reported	1	2
Total	293	479

Table 23. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥18 years to ≤55 years		
Vaccine 30 µg		
Racial origin		
White	8806	15340
Black or African American	1087	1899
Asian	619	1136
American Indian or Alaska Native	128	236
Native Hawaiian or other Pacific Islander	17	32
Multiracial	405	781
Not reported	70	127
Total	11132	19551
Ethnic origin		
Hispanic/Latino	3441	5300
Non-Hispanic/non-Latino	7635	14157
Not reported	56	94
Total	11132	19551
>55 years to ≤64 years		
Vaccine 30 µg		
Racial origin		
White	3416	6271
Black or African American	331	592
Asian	120	227
American Indian or Alaska Native	35	67
Native Hawaiian or other Pacific Islander	4	7
Multiracial	63	120
Not reported	16	31
Total	3985	7315
Ethnic origin		
Hispanic/Latino	901	1560
Non-Hispanic/non-Latino	3067	5724
Not reported	17	31
Total	3985	7315

Table 23. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥65 years to ≤74 years		
Vaccine 30 µg		
Racial origin		
White	3093	6076
Black or African American	187	360
Asian	78	154
American Indian or Alaska Native	20	39
Native Hawaiian or other Pacific Islander	6	12
Multiracial	22	43
Not reported	8	16
Total	3414	6700
Ethnic origin		
Hispanic/Latino	547	1060
Non-Hispanic/non-Latino	2842	5590
Not reported	25	50
Total	3414	6700
≥75 years to ≤84 years		
Vaccine 30 µg		
Racial origin		
White	752	1483
Black or African American	22	42
Asian	17	34
American Indian or Alaska Native	4	8
Multiracial	6	12
Not reported	5	10
Total	806	1589
Ethnic origin		
Hispanic/Latino	89	174
Non-Hispanic/non-Latino	706	1393
Not reported	11	22
Total	806	1589

Table 23. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥85 years		
Vaccine 30 µg		
Racial origin		
White	15	29
Asian	1	2
Multiracial	1	2
Total	17	33
Ethnic origin		
Non-Hispanic/non-Latino	17	33
Total	17	33

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: 27MAR2021 (12:46) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s942_open

Table 24. 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 ≤64 years		
Vaccine 1 µg		
Racial Origin		
White	12	23
Total	12	23
Ethnic Origin		
Non-Hispanic/non-Latino	12	23
Total	2	23
Vaccine 3 µg		
Racial Origin		
White	12	24
Total	12	24
Ethnic Origin		
Non-Hispanic/non-Latino	12	24
Total	12	24
Vaccine 10 µg		
Racial Origin		
White	18	35
Total	18	35
Ethnic Origin		
Non-Hispanic/non-Latino	18	35
Total	18	35
Vaccine 20 µg		
Racial Origin		
White	18	35
Total	18	35
Ethnic Origin		
Non-Hispanic/non-Latino	18	35
Total	18	35
Vaccine 30 µg		
Racial Origin		
White	18	36
Total	18	36
Ethnic Origin		
Non-Hispanic/non-Latino	18	36
Total	18	36

Table 24. 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
≥65 to ≤74 years		
Vaccine 10 µg		
Racial Origin		
White	5	10
Total	5	10
Ethnic Origin		
Non-Hispanic/non-Latino	5	10
Total	5	10
Vaccine 20 µg		
Racial Origin		
White	6	12
Total	6	12
Ethnic Origin		
Non-Hispanic/non-Latino	6	12
Total	6	12
Vaccine 30 µg		
Racial Origin		
White	6	12
Total	6	12
Ethnic Origin		
Non-Hispanic/non-Latino	6	12
Total	6	12

Table 24. 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
≥75 to ≤84 years		
Vaccine 10 µg		
Racial Origin		
White	1	2
Total	1	2
Ethnic Origin		
Non-Hispanic/non-Latino	1	2
Total	1	2
Vaccine 20 µg		
Racial Origin		
White	1	2
Total	1	2
Ethnic Origin		
Non-Hispanic/non-Latino	1	2
Total	1	2

Only race, ethnic origins collected on the case report form with a count of at least one in either column are displayed.
PFIZER CONFIDENTIAL SDTM Creation: 24NOV2020 (15:06) Source Data: adsl Table Generation: 10MAR2021 (12:15) (Cutoff date:23OCT2020, Snapshot Date: 23OCT2020)
Output File: ex_b2_age_dose_race.rtf

Table 25. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

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

Table 25. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

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

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

Table 26. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period –Subjects Who Originally Received BNT162b2

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg		
Racial origin		
White	74	74
Black or African American	2	2
Asian	3	3
American Indian or Alaska Native	10	10
Total	89	89
Ethnic origin		
Hispanic/Latino	46	46
Non-Hispanic/non-Latino	43	43
Total	89	89

Note: 30 µg includes data from phase 1 and phase 2/3.
Note: Subjects who received 2nd Dose of BNT162b2 after unblinding.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:47) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adsl_s9523

Table 27. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001) – Open-Label Follow-up Period –Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

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

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

Table 28. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

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

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

Table 29. 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 30. 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

Table 31. Exposure to BNT162b2 (30 µg) by Special Population (C4591001) – Blinded Placebo-Controlled Follow-up Period

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

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

Table 32. Exposure to BNT162b2 (30 µg) by Special Population (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

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

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

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 starting from 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 33. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	There is limited experience with use of COVID-19 mRNA vaccine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development. Administration of COVID-19 mRNA vaccine in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. **Participants 12 to 15 years of age** Through the cut-off date of 13 March 2021, there were no cases of pregnancies. **Participants 16 years of age and older** Through the DLP of 13 March 2021, there were 50 cases (52 events) originating from Study C4591001, and all were unique pregnancies.
Breastfeeding women	Breastfeeding women were not initially included in the COVID-19 mRNA vaccine clinical development program. It is unknown whether COVID-19 mRNA vaccine is excreted in human milk. The developmental and health benefits of breastfeeding should be

Table 33. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Breastfeeding women *(Cont'd)*	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 vaccines, the underlying maternal condition is susceptible to disease prevented by the vaccine. **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 16 years of age and older** Through the DLP 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 12 to 15 years of age** Please refer to Table 29 and Table 30 for the exposure of special populations. **Participants 16 years of age and older** Please refer to Table 31 and Table 32 for the exposure of special populations.
Population with relevant different ethnic origin/race	Please refer to Table 21 to Table 28 for exposure information by ethnic origin/race from the studies.
Subpopulations carrying relevant genetic polymorphisms	No data available.
Paediatric participants	The safety and efficacy of COVID-19 mRNA vaccine in children and adolescents aged less than 2 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 9 and Table 11).

Table 33. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
	Participants 16 years of age and older Six hundred and seventy one (671) paediatric participants 16 to 17 years of age received COVID-19 mRNA vaccine through the DLP of 13 March 2021 (Table 9 and Table 11).
Elderly (≥65 years old)	Clinical studies of COVID-19 mRNA vaccine included a total of 8846 participants 65 years of age and over; of these, 8827 were from study C4591001, through the cut-off date of 13 March 2021: • 4590 participants in the blinded-placebo controlled follow-up period (Table 9) • 4237 participants in the open-label follow-up period after unblinding (Table 11) Nineteen (19) participants 65 years of age and over were from study BNT162-01 study through the cut-off date of 23 October 2020 (Table 12).

Abbreviations: BMI = body mass index; CT = clinical trial; DLP = data lock point.

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 34.

Table 34. 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.

Cumulatively, through 18 June 2021, approximately 774.478.440 doses of COMIRNATY were shipped worldwide, corresponding to 642,817,105 estimated administered doses.

The worldwide number of shipped doses may serve as a reasonable indicator of subject exposure, considering that approximately 83% of the shipped doses were administered. This ratio represents the proportion of doses cumulatively administered (as per public available data for the EEA[2] countries and the US[3]) out of those cumulatively shipped (based on MAH data according to the shipment tracker [Order Book][4]).

[2] Approximately 83% of the doses shipped in the EU-EEA countries were administered; this proportion has been calculated considering, out of total number of vaccine doses distributed in the EU-EEA countries, the total number of vaccine doses administered as per report on https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab, as of 18 June 2021.

[3] Approximately 83.9% of the doses shipped in the US were administered; this proportion has been calculated considering, out of total number of vaccine doses distributed in the US, the total number of vaccine doses administered as per report on https://covid.cdc.gov/covid-data-tracker/#vaccinations, as of 18 June 2021.

[4] The Order Book is the most accurate tracker of shipment used as data source for all the Regions and Countries; US shipment data not available in the Order Book were taken from the Order Management Dashboard and data for Hong Kong, Macau and Germany were provided by BioNTech.

Data about the number of COMIRNATY doses administered is available for EEA, Japan and US. COMIRNATY exposure data by age group is available for some EEA countries and for Japan (elderly and health workers, Table 37). Currently there are no available public data that allow to estimate the COMIRNATY exposure by gender.

Cumulative worldwide estimated exposure[5] by dose, and region based on or extrapolated from internal data (number of shipped doses) and published data (number of doses administered) is displayed in Table 35.

Table 35. Cumulative Estimated Shipped and Administered Doses of COMIRNATY by Region Worldwide, through 18 June 2021

Region/Country/Other	% of Doses	Total Number of Shipped Doses	Total Number of Administered Doses
Europe	41.8	323502270	268506884
European Union[a] (27)	33.3	257628345	213831526
Additional EEA Countries[a] (3)	0.5	3559335	2954248
Other Countries[b]	8.0	62314590	51721110
North America[c]	29.8	230593605	191392692
US	26.6	205645305	170685603
Canada	3.2	24948300	20707089
Central and South America[d]	7.4	57644730	47845126
Asia	19.5	150739485	125113773
Japan[a]	12.2	94169790	78160926
Other Countries[e]	7.3	56569695	46952847
Oceania	0.7	5681520	4715662
Australia/New Zealand[a]	0.7	5681520	4715662
Other Countries	0.0	0	0
Africa[f]	0.8	6316830	5242969
Total	**100.0**	**774478440**	**642817105**

[5] Including data from license partners.

Table 35. Cumulative Estimated Shipped and Administered Doses of COMIRNATY by Region Worldwide, through 18 June 2021

Region/Country/Other	% of Doses	Total Number of Shipped Doses	Total Number of Administered Doses

a. Conditional approval.
b. Includes:
UK, with both authorisation for emergency supply under regulation 174 and the conditional marketing authorisation approval,
Albania, Kosovo, North Macedonia and Switzerland with conditional approval,
Georgia, Serbia and Ukraine with authorization for emergency supply,
Azerbaijan, Bosnia and Moldova where BNT162b2 was shipped for COVAX,
Turkey where it was shipped according to a pharmacovigilance agreement in place by the MAH and the Turkish government.
c. Authorization for emergency supply.
d. Includes:
Brazil and Peru with conditional approval,
Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Honduras, Mexico, Panama and Uruguay with authorisation for emergency supply,
Bolivia where BNT162b2 was shipped for COVAX;
e. Includes:
Hong Kong, Malaysia and South Korea with conditional approval,
Bahrain, Iraq, Israel, Jordan, Kuwait, Lebanon, Macau, Oman, Palestine, Pakistan, Qatar, Saudi Arabia, Singapore, Sri Lanka and United Arab Emirates with authorization for emergency supply,
Bangladesh, Bhutan, Laos, Maldives, Mongolia, Philippines and West Bank & Gaza where BNT162b2 was shipped for COVAX;
f. Includes:
Rwanda, Tunisia and South Africa where BNT162b2 received authorisation for emergency supply,
Angola, Botswana, Cape Verde, Chad, Ivory Coast, Libya and Togo where BNT162b2 was shipped for COVAX.

Out of the total shipped and administered doses, 213,475,665 and 177,184,802 respectively, were shipped to Rest Of World (Non EEA countries, Canada, Central and South America, Asian countries [excluding Japan], Oceania and Africa).

The EEA published data (number of administered doses, number of doses administered as 1st dose and 2nd dose by country)[6] are summarized in Table 36.

[6] Approximately 83% of the doses shipped in the EU-EEA countries were administered; this proportion has been calculated considering, out of total number of vaccine doses distributed in the EU-EEA countries, the total number of vaccine doses administered as per report on https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab, as of 18 June 2021.

Table 36. EEA - Cumulative and Interval Number of Administered Doses by Age Group and Dose 1 and Dose 2

Countries	**<18 years**		**18-24 years**		**25-49 years**		**50-59 years**		**60-69 years**		**70-79 years**		**≥80 years**		**All**[b]	
	Dose 1	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*
Austria			167555	47702	971199	342616	641838	314720	546224	395763	393795	343964	355207	333226	3135921	1785206
Belgium			166728	64131	1408198	429906	849729	432004	840119	736020	536927	523117	379786	368636	4193346	2557731
Bulgaria	266	189	15278	11513	159468	133713	99168	85240	121185	102251	92622	76077	28906	23204	517254	432452
Croatia	2280	255	42259	8569	317338	102782	198754	84438	222771	128620	135422	96913	60943	47868	977487	469190
Cyprus			17984	10944	116794	78519	47914	42806	38710	34614	23140	18821	25185	23655	269737	209366
Czechia	16771	521	124179	27930	1465870	351932	727173	335423	730020	551387	545166	488903	247876	233858	3843810	1990215
Denmark			160444	22357	447539	156710	629283	113376	555667	406034	518812	509466	238233	235276	2550785	1443219
Estonia	2738	217	19446	4813	121570	46108	56404	41242	51754	43140	56113	51820	41253	38412	346867	225631
Finland			61362	8770	831073	85286	481133	71374	348956	69582	449416	240046	256030	236973	2427970	712031
France															24326612	1286871 5
Germany															28250232	2047252 9
Greece			26492	14949	771439	360626	699135	528149	476183	383765	599397	555891	501387	479715	3090855	2331578
Hungary	14085 3	80059	163126	76516	867158	595910	310562	251589	370538	333408	307408	291502	203466	195665	2360581	1828050
Iceland			12113	3307	50143	27544	16532	14965	14290	13542	9173	8743	12410	12334	114697	80434
Ireland			41574	22891	529757	182446	341416	243352	78469	60161	306069	278298	169889	158073	1472938	948542
Italy	23619 9	4016	911472	228860	5613161	181164 1	4626670	172722 3	3069219	2100315	2426244	2010958	3490947	3320810	20902474	1121284 3
Latvia			22531	15621	114418	96539	40493	33501	31994	25690	14130	11102	6068	4803	263132	204368
Liechtenstei n															5483	3831
Lithuania	13981	707	56909	26792	255693	171088	141155	120218	152207	139020	99695	94176	57027	48916	764295	600966
Luxembourg			1520	1239	73003	18864	50700	48169	31139	30120	13128	12717	18550	18135	194297	134808
Malta			18843	12790	89993	78043	21670	21705	18653	19610	36278	37112	21583	19858	207544	193777
Netherlands															6213306	3484049
Norway															1306486	937807
Poland			608505	197615	3690822	195159 4	1702115	122078 0	1931938	1542381	1966597	1836281	961394	915070	11251269	7683325
Portugal	2201	765	33504	25324	693279	315197	749493	298839	598816	511126	477845	445734	575661	552248	3128600	2148468
Romania	26558	23235	266386	219774	1309771	121981 6	644430	609328	750019	718764	444435	426774	146176	138833	3589468	3355093
Slovakia			75234	28771	457959	250535	169916	127800	249662	220386	231902	219288	82806	77104	1267479	923884
Slovenia	5059	726	17768	5571	114339	59404	94655	72449	106076	92438	99017	91676	67672	61190	499527	382728
Spain	4641	2745	105814	84748	3436349	868561	4278583	254956 9	1051898	969309	3513927	3448266	2680133	2635045	15071210	1055819 1

Table 36. EEA - Cumulative and Interval Number of Administered Doses by Age Group and Dose 1 and Dose 2

Countries	**<18 years**		**18-24 years**		**25-49 years**		**50-59 years**		**60-69 years**		**70-79 years**		**≥80 years**		**All[b]**	
	Dose 1	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*	*Dose 1*	*Dose 2*
Sweden			59666	35857	703182	238904	814215	267874	695462	577755	557804	527731	424263	403758	3254592	2051890
Grand Total	451547	113435	3196692	1207354	24609515	9974284	18433136	9656133	13081969	10205201	13854462	12645376	11052851	10582665	14579825	9223091

a. Source is https://covid19-vaccine-report.ecdc.europa.eu/ (point 6, cumulative period as of week 24, 2021).
b. Population may include also subjects of unknown age.

Table 37. Japan - Cumulative and Interval Number of Administered Doses by Health Workers and Elderly and Dose (1st and 2nd)

Dose Number			
	1st Dose	*2nd Dose*	*Total*
Elderly	16,308,903	4,834,436	21,143,339
Medical workers	5,463,305	4,320,082	9,783,387
Total	**21,772,208**	**9,154,518**	**30,926,726**

Source: PMDA website https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html
(English site: https://japan.kantei.go.jp/ongoingtopics/vaccine.html)
Data split by Tradename and dose (1st and 2nd) is only available on the Japanese website, and not on the English website.
Data downloaded on 21 June 2021.

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 systemic 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 38.

Table 38. 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, Pyrexia, Chills, Fatigue, Headache, Myalgia, and Arthralgia.

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

Participants 16 years of age and older

The reactogenicity data were collected by participants' e-diary for reporting prompted local reactions and systemic events for 7 days after each dose.

Local Reactions

- Phase 1, Study BNT162-01

Local reactions generally increased in frequency and/or severity with increasing dose level and number of doses of COVID-19 mRNA vaccine. Most local reactions were mild or moderate in severity and resolved within several days of onset. For COVID-19 mRNA vaccine, incidence of local reactions was generally less after each dose in the older group (56-85 years) compared with the younger group (18-55 years), and severity of reactions was similar between both age groups.

- Phase 3, Study C4591001

In the COVID-19 mRNA vaccine 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 COVID-19 mRNA in the younger group (83.7% vs 78.3%) and in the older group (70.1% vs 66.1%).

In the COVID-19 mRNA vaccine 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 COVID-19 mRNA vaccine in the younger age group (5.4% vs 5.6%) and in the older age group (5.3% vs 7.2%). Frequencies of swelling were similar after Dose 1 compared with Dose 2 of COVID-19 mRNA vaccine in the younger age group (6.3% vs 6.8%, respectively) and in the older age group (7.0% vs 7.8%). In the placebo group, redness and swelling were reported infrequently in the younger (≤1.0%) and older (≤1.2%) 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. Severe redness and swelling were reported infrequently and were similar between the younger and older age groups (≤0.7) after any dose. Severe pain at the injection site occurred more frequently in the younger age group compared to the older age group (2.5% vs 0.7%). After the first and second dose and in both age groups, the majority of local reactions were mild or moderate in severity, and no Grade 4 local reactions were reported.

The median onset for local reactions after either dose was between Day 1.0 and Day 2.0 (Day 1.0 was the day of vaccination) in the younger age group and between Day 1.0 and Day 3.0 in the older age group. Local reactions resolved with median durations between 1.0 and 2.0 days in both age groups.

For local reactions the frequency of redness, swelling, and pain at the injection site after any dose of COVID-19 mRNA vaccine was 8.5%, 10.2%, and 80.2% compared with 9.9%, 11.1%, and 84.5% for those SARS-CoV-2 positive and negative at baseline, respectively. While the frequency of local reactions was numerically higher in those negative at baseline, these differences are not clinically meaningful.

Systemic Events

- Phase 1, Study BNT162-01

Systemic events generally increased in frequency and/or severity with increasing dose level and number of doses of COVID-19 mRNA vaccine. Most systemic events were mild or

moderate, arose within the first 1 to 2 days after dosing, and were short-lived. For COVID-19 mRNA vaccine, the incidence of systemic events after each dose was similar in the older group (56-85 years) compared with the younger group (18-55 years). Reports of severe systemic events were similar between the younger and older COVID-19 mRNA vaccine groups.

- Phase 3, Study C4591001

Systemic events were generally increased in frequency and severity in the younger group (16-55 years of age) compared with the older group (>55 years), with frequencies and severity increasing with number of doses (Dose 1 vs Dose 2). Vomiting and diarrhoea were exceptions, which were reported similarly infrequently in both age groups and 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 (49.4% vs 61.5%) compared to older group (33.7% vs 51.0%)
- headache: younger group (43.5% vs 54.0%) compared to older group (25.0% vs 39.4%)
- myalgia: younger group (22.9% vs 39.3%) compared to older group (13.6% vs 28.9%)
- chills: younger group (16.5% vs 37.8%) compared to older group (6.5% vs 23.4%)
- arthralgia: younger group (11.8% vs 23.8%) compared to older group (8.7% vs 19.0%)
- pyrexia: younger group (4.1% vs 16.4%) compared to older group (1.3% vs 11.8%)
- vomiting: younger group (1.2% vs 2.2%) compared to the older group (0.5% vs 0.7%)
- diarrhoea: younger group (10.7% vs 10.0%) compared to the older group (8.4% vs 8.2%).

Systemic events were generally reported less frequently in the placebo group than in the COVID-19 mRNA vaccine 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 COVID-19 mRNA vaccine group. In the older age group, vomiting and diarrhoea (after Dose 1 and Dose 2) were reported at similar frequencies in the placebo group and the COVID-19 mRNA vaccine group.

Following both Dose 1 and Dose 2, use of antipyretic/pain medication was slightly less frequent in the older age group (19.0% vs 37.0%) than in the younger age group (27.8% vs 45.2%) 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 COVID-19 mRNA vaccine group and was similar after Dose 1 and Dose 2 in the younger and older placebo groups (ranging from 9.3% to 13.7%).

Severe pyrexia (>38.9°C to 40.0°C) increased in frequency with the number of doses (Dose 1 versus Dose 2) in younger (0.3% vs 1.5%) and older (0.0% vs 0.4%) participants who received COVID-19 mRNA vaccine and was reported in 0.1% of participants who received placebo in both age group after both doses. One participant in the younger COVID-19 mRNA vaccine group reported pyrexia of 41.2°C only on Day 2 after Dose 2 and was nonfebrile for all other days of the reporting period. Grade 4 pyrexia was not reported in the older COVID-19 mRNA vaccine group or in any placebo participants.

After the first and second dose and in both age groups, the majority of systemic events were mild or moderate in severity.

Systemic events in the younger and older age groups after either dose had a median onset day between Day 2.0 and Day 4.0 (Day 1.0 was the day of vaccination) and resolved with a median duration of 1 day in both age groups.

For any pyrexia (mild, moderate, severe or grade 4) after either dose there were 17.5% compared to 15.1% in those positive and negative for SARS-CoV-2 at baseline, respectively. Severe pyrexia (>38.9°C to 40.0°C) was reported in 0.6% participants and 1.0% participants in those positive and negative for SARS-CoV-2 at baseline, respectively. The frequency for other systemic events after any dose was numerically lower for those positive at baseline: fatigue, headache and chills the frequency was 54.2%, 49.7% and 32.8% compared with 65%, 57.4%, 34.7% for those positive and negative for SARS-CoV-2 at baseline, respectively. Arthralgia was another exception where 27.1% compared to 25.0% were reported between those positive and negative for SARS-CoV-2 at baseline. Note that the baseline SARS-CoV-2 positive subgroup included far fewer participants the negative subgroup, so their results should be interpreted with caution.

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 defined taking into consideration the available lists of AESIs from the following expert groups and regulatory authorities:

Brighton Collaboration (SPEAC)[62]

- ACCESS protocol[63]
- US CDC (preliminary list of AESI for VAERS surveillance)[64]
- MHRA (unpublished guideline).

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

terms searched in the safety database to identify cases of potential AESIs are presented by body system (e.g. Cardiovascular, Hepatic, Respiratory, etc.) when possible for ease of presentation. Medical concepts that are captured in the AESI list include:

- Immune and Autoimmune mediated events that are of interest for all vaccinations
- Events associated with severe COVID-19

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 Identified Risk: Myocarditis and Pericarditis

Risk-benefit impact

Myocarditis and pericarditis are serious conditions that may occur concomitantly and that may range in clinical importance from mild to 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 initial 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

COVID-19 mRNA vaccine will be used in individuals who also may receive other vaccines. Studies to determine if co-administration of COVID-19 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 COVID-19 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 COVID-19 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 39. Anaphylaxis

<table>
<tr><td>Potential mechanisms, evidence source and strength of evidence</td><td>Interaction of an allergen with IgE on basophils and mast cells triggers release of histamine, leukotrienes and other mediators that cause diffuse smooth muscle contraction and vasodilation with plasma leakage. This can manifest clinically with dyspnea, hypotension, swelling (sometimes leading to airway compromise), and rash (including hives).</td></tr>
<tr><td>Characterisation of the risk</td><td>Participants 12 to 15 years of age
<u>Data from the CT database</u>[a]
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.

Through 18 June 2021[b] there were no cases reporting Anaphylactic reaction/shock, Anaphylactoid reaction/shock as SAEs from the CT dataset.

<u>Data from the safety database:</u>
Through 28 February 2021, there were no cases reporting anaphylactic reactions in the safety database in the 12 to 15 years of age participants.

Through 18 June 2021[b], there were 5 cases (4 anaphylactic reaction and 1 anaphylactic shock) in individuals 12 to 15 years of age; overall event seriousness and outcome are summarized below:

<table>
<tr><th></th><th>Total Events
N = 5</th></tr>
<tr><td>Serious events</td><td>5</td></tr>
<tr><td>Events with Criterion of Hospitalization</td><td>1</td></tr>
<tr><td colspan="2">Distribution of events by Outcome</td></tr>
<tr><td>Outcome: Death</td><td>0</td></tr>
<tr><td>Outcome: Resolved/Resolving</td><td>3</td></tr>
<tr><td>Outcome: Not resolved</td><td>2</td></tr>
</table>

Participants 16 years of age and older
<u>Data from the CT database:</u>
Data from the ongoing Phase 3 clinical Study C4591001 through the DLP of 13 March 2021 have been reviewed and information pertinent to anaphylactic reactions observed in the study is summarised below:</td></tr>
</table>

Table 39. Anaphylaxis

Characterisation of the risk *(Cont'd)*

Five (5) serious events (Acute respiratory failure, Cardiac arrest, Anaphylactic reaction, Anaphylactoid reaction, and Anaphylactic shock) were reported. The Anaphylactoid reaction was assessed as related to study treatment by the Investigator. The remaining 4 events were deemed not related to study treatment by the Investigator.

Through 18 June 2021, there was 1 case from the CT dataset, from Phase 3 clinical study C4591001, of serious Anaphylactoid reaction in a PPD -year-old participant reported as resolved and deemed related to study treatment by the Investigator.

Data from the safety database through DLP 28 February 2021:

Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, 1833 potentially relevant cases[a], were retrieved from the Anaphylactic reaction SMQ (Narrow and Broad) search strategy, applying the MedDRA algorithm; these cases were individually reviewed and assessed according to Brighton Collaboration (BC) definition and level of diagnostic certainty as shown in the table below:

Brighton Collaboration Level	Number of cases
BC 1	290
BC 2	311
BC 3	10
BC 4	391
BC 5	831
Total	1833

Level 1 indicates a case with the highest level of diagnostic certainty of anaphylaxis, whereas the diagnostic certainty is lowest for Level 3. Level 4 is defined as "reported event of anaphylaxis with insufficient evidence to meet the case definition" and Level 5 as not a case of anaphylaxis.

There were 1002 cases (54.7% of the potentially relevant cases retrieved), 2958 potentially relevant events, from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy, meeting BC Level 1 to 4.

Overall event seriousness and outcome of these 1002 cases are summarized below:

	Total Events N = 2958 (%)
Serious events	2341 (79.1)
Events with Criterion of Hospitalization	752 (25.4)
Distribution of events by Outcome*	
Outcome[∞]: Death[§]	9 (0.3)
Outcome: Resolved/Resolving	1922 (65.0)
Outcome: Not resolved	229 (7.7)
Outcome: Resolved with sequelae	48 (1.6)
Outcome: Unknown/No data	754 (25.5)

Table 39. Anaphylaxis

	*. For the outcome count, the multiple Lowest Level Terms that code to the same PT within a case are counted and presented individually. Therefore, for selected PTs the total count of the event outcome may exceed the total number of events. ∞ Different clinical outcomes may be reported for an event occurred more than once to the same individual. § There were 4 individuals in the anaphylaxis evaluation who died on the same day they were vaccinated. Although these patients experienced adverse events (9) that are potential symptoms of anaphylaxis, they all had serious underlying medical conditions, and one individual appeared to also have COVID-19 pneumonia, that likely contributed to their deaths. The most frequently reported relevant PTs (≥2%), from the Anaphylactic reaction SMQ (Narrow and Broad) search strategy were: Anaphylactic reaction (435), Dyspnoea (356), Rash (190), Pruritus (175), Erythema (159), Urticaria (133), Cough (115), Respiratory distress, Throat tightness (97 each), Swollen tongue (93), Anaphylactic shock (80), Hypotension (72), Chest discomfort (71), Swelling face (70), Pharyngeal swelling (68), Lip swelling (64) and Flushing (58). Data from the safety database through DLP 18 June 2021[b] There were 3822 cases (1.2% of the total post authorization dataset) reporting a total of 3914 events in individuals 16 years and older including: Anaphylactic reaction (3414) Anaphylactic shock (420) Anaphylactoid rection (75) Anaphylactoid shock (5) Overall event seriousness and outcome are summarized below:

	Total Events N = 3914 (%)
Serious events	3868 (98.8)
Events with Criterion of Hospitalization	1231 (31.5)
Distribution of events by Outcome	
Outcome: Death	28 (0.7)
Outcome: Resolved/Resolving	2958 (75.6)
Outcome: Not resolved	171 (4.4)
Outcome: Resolved with sequelae	56 (1.4)
Outcome: Unknown	704 (18)

	Conclusion: Evaluation of BC cases Level 1 – 4 through 28 Feb 2021 and of cases of Anaphylactic reaction/shock, Anaphylactoid reaction/shock through 18 Jun 2021, did not reveal any significant new safety information. Anaphylaxis is appropriately described in the product labeling as are non-anaphylactic hypersensitivity events. Surveillance will continue.
Risk factors and risk groups	Known hypersensitivity to any components of the vaccine.
Preventability	Prevention of anaphylaxis may not be possible, particularly with the 1st dose of a vaccine; therefore, healthcare professionals administering the vaccine must be vigilant for early signs and symptoms.

Table 39. Anaphylaxis

Impact on the risk-benefit balance of the biologic product	Anaphylactic reaction in an individual can be impactful (medically important) because it is a potentially life-threatening event requiring medical intervention.
Public health impact	Minimal due to rarity of the event. Although the potential clinical consequences of an anaphylactic reaction are severe, this is a known risk of vaccines to healthcare professionals with negligible public health impact.

a. Search criteria for cases of anaphylaxis in the safety database have been revised as compared to the RMP version 1.0. The revised search criteria are: Anaphylactic reaction SMQ (Narrow and Broad, with the MedDRA algorithm applied), with relevant cases assessed according to Brighton Collaboration (BC) criteria.
b. Updated search criteria starting from the 6th SMSR (see 5th Monthly Safety Update preliminary PRAC Assessment Report; EMEA/H/C/005735/MEA/002.4): PTs Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, without Brighton Collaboration criteria applied.

Please note that CT dataset from the safety database includes only cases reporting SAEs.

Table 40. Myocarditis and Pericarditis

Potential mechanisms, evidence source and strength of evidence	A mechanism of action (MOA) by which the vaccine could cause myocarditis and pericarditis has not been established. Nonclinical studies, protein sequence analyses and animal studies in rats and non-human primates have not identified a MOA. Hypotheses for MOA include an immune stimulated response (including the possibility of molecular mimicry), a general systemic inflammatory response from vaccination or a hypersensitivity response.
Characterisation of the risk	***Participants 12 to 15 years of age*** **Data from the CT dataset[a]:** There were no cases reporting Myocarditis or Pericarditis as SAE in the clinical trial dataset through the cut-off date of 18 June 2021. **Data from the safety dataset[a]:** Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 18 June 2021, there were 15 potentially relevant cases of Myocarditis and Pericarditis: 13 cases reported myocarditis and 4 cases reported pericarditis (in 2 of these 15 cases, the subjects developed both myocarditis and pericarditis). Myocarditis (13 cases) These 13 cases were individually reviewed and assessed according to Brighton Collaboration (BC) Myocarditis Case Definition and Level of Certainty Classification (version 1.4.2, 30 May 2021), as per table below:

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

Table 40. Myocarditis and Pericarditis

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

No cases met BC levels 1 to 3. Overall event seriousness and outcome of the 11 cases meeting BC Level 4 cases are summarized below:

	Total Events N = 11
Serious events	10
Events with Criterion of Hospitalization	9
Distribution of events by Outcome	
Outcome: Death	0
Outcome: Resolved/Resolving	3
Outcome: Not resolved	4
Outcome: Resolved with sequelae	0
Outcome: Unknown/No data	4

Pericarditis (4 cases)

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

	Total Events N = 4
Serious events	3
Events with Criterion of Hospitalization	1
Distribution of events by Outcome	
Outcome: Death	0
Outcome: Resolved/Resolving	1
Outcome: Not resolved	1
Outcome: Resolved with sequelae	0
Outcome: Unknown/No data	2

Participants 16 years of age and older

Data from the CT dataset[a]

There were two cases reporting myocarditis and pericarditis as SAEs in the clinical trial dataset through the cut-off date of 18 June 2021. These cases originated from Phase 3 clinical study C4591001 and are summarized below:

Myocarditis: there were no cases of myocarditis as SAE.

Pericarditis (2 cases):

Two (2) serious adverse events [PT Pericarditis] were reported, both deemed not related to study treatment by the Investigator.

Data from the safety dataset[a]:

Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 18 June 2021, there were 823 potentially relevant cases (0.3% of the total post-authorization dataset): 490 cases reported myocarditis and 371 cases reported pericarditis (in 38 of these 823 cases, the subjects were reported to have developed both myocarditis and pericarditis).

Table 40. Myocarditis and Pericarditis

Myocarditis (490 cases):

These 490 cases were individually reviewed and assessed according to BC Myocarditis Case Definition and Level of Certainty Classification (version 1.4.2, 30 May 2021), as shown in the table below:

Brighton Collaboration Level	Number of cases
BC 1	41
BC 2	44
BC 3	42
BC 4	337
BC 5	26
Total	490

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

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

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

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

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

Pericarditis (371 cases)

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

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

	Total Events N = 372 (%)
Serious events	370 (99.5)
Events with Criterion of Hospitalization	206 (55.4)
Distribution of events by Outcome	
Outcome: Death	3 (0.8)
Outcome: Resolved/Resolving	213 (57.3)
Outcome: Not resolved	63 (16.9)
Outcome: Resolved with sequelae	7 (1.9)
Outcome: Unknown/No data	86 (23.1)

Conclusion: the MAH has updated the labels to include information about myocarditis and pericarditis following vaccine administration as well as has

Table 40. Myocarditis and Pericarditis

	distributed a Direct Healthcare Professional Communication (DHPC) to address these findings. Surveillance will continue.
Risk factors and risk groups	Post-authorization reports have been received for more males than females, over a wide age range and following dose 1 and dose 2 of the vaccine. Evaluation by the EU and US CDC has found reports to be most frequent in adolescent and young adult male patients following the second dose of vaccine.
Preventability	Due to an unknown MOA, preventative measures cannot be indicated.
Impact on the risk-benefit balance of the biologic product	The vaccine continues to have a favorable risk benefit balance
Public health impact	Considering the low rates of myocarditis and pericarditis reported following vaccination, balanced with the risk of death and illness (including myocarditis) caused by SARS-CoV-2, the public health impact of post-vaccination myocarditis and pericarditis is minimal.

a. Search criteria: the following PTs were used to retrieve cases of Myocarditis and Pericarditis: Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis; Autoimmune pericarditis, Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

Please note that CT dataset from the safety database includes only cases reporting SAEs.

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

Table 41. 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.[57,65] 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.[66] Potential mechanisms of enhanced disease may include both T cell-mediated [an immunopathological response favouring T helper cell type 2 (T_h2) over T helper cell type 1 (T_h1)] 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).[67]
Characterisation of the risk	***Participants 12 to 15 years of age*** Data from the CT database There were no cases of VAED/VAERD as shown in the table below:

Table 41. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Characterisation of the risk *(Cont'd)*

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

Timing	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	BNT162b2 (30 µg) (N[a]=1131) (95% CI[c])	Placebo (N[a]=1129) n[b] (%)	Placebo (N[a]=1129) (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

There were no cases reporting VAED/VAERD as SAEs in the CT dataset[a] through the DLP of 18 June 2021.

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.

Through the updated DLP 18 June 2021, there were no cases indicative of VAED or VAERD in the safety database involving individuals 12 to 15 years of age.

Participants 16 years of age and older

Data from the CT database:

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

Timing	BNT162b2 (30 µg) (N[a]=23164) n[b] (%)	BNT162b2 (30 µg) (N[a]=23164) (95% CI[c])	Placebo (N[a]=23155) n[b] (%)	Placebo (N[a]=23155) (95% CI[c])
PD1 Before Dose 2	0	(0.0, 0.0)	6 (0.0)	(0.0, 0.1)
Within 7 days PD1	0	(0.0, 0.0)	0	(0.0, 0.0)
PD2	1 (0.0)	(0.0, 0.0)	25 (0.1)	(0.1, 0.2)
Within 7 days PD2	0	(0.0, 0.0)	2 (0.0)	(0.0, 0.0)

Table 41. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Total[d]	1 (0.0)	(0.0, 0.0)	31 (0.1)	(0.1, 0.2)	

Note: This table includes subjects from Phase 2/3 only.
Abbreviations: PD1 = post-dose 1; PD2 = post-dose 2.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Total is the sum of PD1 and PD2.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adc19ef Table Generation: 27MAR2021 (12:47) (Cutoff date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_PVP_BLA/adeff_s901

If VAED/VAERD were to occur in vaccinated individuals, it may manifest as a modified and/or more severe clinical presentation of SARS-CoV-2 viral infection upon subsequent natural infection. This may result in individuals assumed to be at lower risk for severe COVID-19 having more severe disease, for individuals at known risk for severe COVID-19 (e.g. older or immunocompromised) having higher rates of fatal outcomes, or for observation of an 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,[68] 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.

There were no cases indicative of VAED/VAERD as SAEs in the CT dataset through the DLP of 18 June 2021.

Data from the safety database through DLP 28 February 2021:

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

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

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

One hundred and thirty-eight (138) cases [0.25% of the total Post-authorization dataset], reporting 317 potentially relevant events.

Seriousness criteria for the total 138 cases: Medically significant (71, of which 8 also serious for disability), Hospitalization required (non-fatal/non-life threatening) (16, of which 1 also serious for disability), Life threatening (13, of which 7 were also serious for hospitalization), Death (38).

Table 41. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Gender: Females (73), Males (57), Unknown (8);

Age (n=132) ranged from 21 to 100 years (mean = 59.7 years, median = 60.0);

Overall event seriousness and outcome are summarized below.

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

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

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

Through the updated DLP 18 June 2021, there were 584 cases (0.2% of the total post-authorization dataset), reporting 1427 potentially relevant events.

Seriousness criteria for the total 584 cases: Medically significant (452, of which 10 also serious for disability), Hospitalization required (non-fatal/non-life threatening) (115, of which 3 also serious for disability), Life threatening (34, of which 22 were also serious for hospitalization), Death (160).

Gender: Females (298), Males (268), Unknown (18);

Age (n=553) ranged from 17 to 103 years (mean = 70.3 years, median = 77.0);

Overall event seriousness and outcome are summarized below:

	Total Events N = 1427 (%)
Serious events	1261 (88.4)
Events with Criterion of Hospitalization	612 (42.9)
Distribution of events by Outcome[a]	
Outcome: Death	311 (21.8)
Outcome: Resolved/Resolving	375 (26.3)
Outcome: Not resolved	246 (17.2)
Outcome: Resolved with sequelae	14 (1.0)
Outcome: Unknown/No data	484 (33.9)

Table 41. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

	a. For the outcome count, the multiple Lowest Level Terms that code to the same PT within a case are counted and presented individually. Therefore, for selected PTs the total count of the event outcome may exceed the total number of events. The most frequently reported relevant PTs (≥2%) were: Drug ineffective (390), Vaccination failure (194), Dyspnoea (180), COVID-19 pneumonia (179), Diarrhoea (111), Respiratory failure (52), Vomiting (50), Pulmonary embolism (33). Conclusion: VAED may present as severe or unusual clinical manifestations of COVID-19. Overall, there were 37 subjects with suspected COVID-19 and 101 subjects with confirmed COVID-19 following one or both doses of the vaccine; 75 of the 101 cases were severe, resulting in hospitalisation, disability, life threatening consequences or death. None of the 75 cases could be definitively considered as VAED/VAERD. In the updated review, overall, there were 425 subjects with confirmed COVID 19 following one or both doses of the vaccine; 288 of the 425 cases were severe, resulting in hospitalization, disability, life threatening consequences or death. None of the 288 cases could be definitively considered as VAED/VAERD. The review of subjects with COVID-19 following vaccination, based on the current evidence, VAED/VAERD may remain a theoretical risk for the vaccine. Surveillance will continue.
Risk factors and risk groups	It is postulated that the potential risk may be increased in individuals producing lower neutralizing antibody titers or in those demonstrating waning immunity.[67,68]

Table 41. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Preventability	An effective vaccine against COVID-19 that produces high neutralizing titers and a T_H1 predominant $CD4^+$ T cell response and strong $CD8^+$ T cell response, is expected to mitigate the risk of VAED/VAERD;[57,67] that immune profile is elicited by COVID-19 mRNA vaccine in clinical and preclinical studies.[69,70]
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 the RMP version 1.0. The revised 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).

Please note that CT dataset from the safety database includes only cases reporting SAEs.

SVII.3.2. Presentation of the Missing Information

Table 42. 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 initial 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 characterization:
The lack of data is communicated in product labelling; for clinical study of the safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women and while breast feeding, see PART III.2 and PART III.3.

Table 43. 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 PART III.2 and PART III.3).

Table 44. 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 (see PART III.2 and PART III.3).

Table 45. 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 (see PART III.2 and PART III.3).

Table 46. Interaction with other Vaccines

Evidence source:
There are no data on interaction of COVID-19 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 (see PART III.2 and PART III.3).

Table 47. 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 COVID-19 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 COVID-19 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 48. Summary of Safety Concerns

Important Identified Risks	Anaphylaxis Myocarditis and Pericarditis
Important Potential Risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use in pregnancy and 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 updated version of the DCA is provided in Annex 4;
  - potential anaphylactic reactions in individuals who have received the COVID-19 mRNA vaccine. The DCA is provided in Annex 4.
- 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.

- The web-based AE reporting portal www.pfizersafetyreporting.com 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, were 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 utilized 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" were made available to vaccinators in the member states where utilisation of a nationally mandated vaccination card is not required.

- 29 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 16 studies, of which 3 global, 5 in Europe only, and 7 in US only; the countries where 1 study is planned to be conducted are not available at this time. There are 6 Interventional studies (C4591001, C4591015, BNT162-01 Cohort 13, C4591018, C4591024 and 1 study for vaccine interactions), 2 Low-Interventional studies (WI235284 and WI255886) and 8 Non-Interventional studies (7 safety and 1 effectiveness), summarised in the table below and further detailed in Table 49 and Table 50.

Study Number	Country	Interventional/ Non-Interventional	Purpose
C4591001	Global	Interventional	Safety
C4591015	Global	Interventional	Safety
C4591009	US	Non-Interventional	Safety
C4591010	EU	Non-Interventional	Safety
C4591011	US	Non-Interventional	Safety
C4591012	US	Non-Interventional	Safety
C4591021 (former ACCESS/VAC4EU)	EU	Non-Interventional	Safety
C4591038 (former C4591021 substudy)	EU	Non-Interventional	Safety
C4591036 (former Pediatric Heart Network)	US	Non-Interventional	Safety
C4591014	US	Non-Interventional	Effectiveness[a]
WI235284	US	Low-Interventional[c]	Effectiveness[a]
WI255886	EU[b]	Low-Interventional[c]	Effectiveness[a]
BNT162-01 Cohort 13	EU	Interventional	Safety
C4591018[d]	US	Interventional	Safety
C4591024 (former Safety and immunogenicity in high risk adults)	Global	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. United Kingdom.
c. 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'.
d. The enrolment into the study became highly problematic after the CDC Advisory Committee on Immunisation Practices (ACIP) recommendation for the prioritization of immunisation of high-risk individuals such as younger adults with high-risk medical conditions including autoimmune disease undergoing immunomodulator treatment (tofacitinib and TNF inhibitors). To address the commitment, (as per procedure PAM-MEA-015) due to the anticipated challenges in the timely enrolment of individuals with rheumatoid arthritis in study C4591018, a decision was made to replace the study C4591018 with increasing the number of immunocompromised participants in study C4591024 to a number comparable to that initially planned across the 2 studies.

Non-Interventional Post Approval Safety Studies (7)

- The MAA proposes 6 complementary studies of real-world safety of COVID-19 mRNA vaccine that use multiple data sources and study designs. These are described in Table 49 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.

- Study C4591021 is a Comirnaty safety surveillance study conducted in collaboration with University Medical Center Utrecht on behalf of Vaccine Monitoring Collaboration for Europe Consortium research team VAC4EU and based on the master surveillance protocol.

- Additionally, C4591038 (formally known as the C4591021 substudy) is also a collaboration with University Medical Center Utrecht on behalf of VAC4EU Consortium research team and is designed as a substudy of C4591021 to assess the natural history of post-vaccination myo-/pericarditis, e.g., recovery status (using medical record review) and/or identification of serious cardiovascular outcomes (using existing structured data) within 1 year of myo-/pericarditis diagnosis among occurring in individuals vaccinated with COMIRNATY as well as individuals not vaccinated with a COVID-19 vaccine.

- In addition to the studies in the EU, in support of the US EUA application, Pfizer will conduct 3 US studies for safety surveillance of COVID-19 mRNA. These studies include:

    - 1 study using secondary data from administrative claims/electronic medical records for military and civilian personnel and their families in the Department of Defense Military Health System (C4591011).

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

    - 1 study using secondary data from administrative claims and electronic health records from data research partners participating in the US Sentinel System (C4591009).

    - 1 study using primary data from the Pediatric Heart Network (PHN), a NIH-funded consortium of hospitals to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis over a 5 year period. A full protocol will be shared by 30 November 2021 (C4591036).

- The protocols for the safety studies in the US (C4591009, C4591011 and C4591012) were added in Annex 3 Part C.

Non-Interventional Post-Approval Safety Studies Assessing Myocarditis/Pericarditis

Studies C4591021(EU), C4591038 (former C4591021 substudy) (EU), C4591011 (US), C4591012 (US), and C4591009 (US) will describe the incidence of myocarditis/pericarditis following Comirnaty vaccination overall, and stratified by age group, gender, race/ethnicity (if feasible), dose, and risk interval using structured information and following case confirmation via medical record review where feasible. To assess the magnitude of risk, these studies include comparative methods (self-controlled analyses, and analyses involving a separate comparator group).

Relative risk (RR) estimates from comparative analyses will be obtained overall and stratified by the same factors as described above when supported by sufficient cell counts.

To evaluate long-term outcomes, myocarditis/pericarditis-specific analytic endpoints in currently planned or ongoing studies C4591009, C4591011, C4591012, C4591021 and C4591038 (former C4591021 substudy) will assess the natural history of post-vaccination myo-/pericarditis, e.g., recovery status (medical record review) and/or identification of serious cardiovascular outcomes (structured data) within 1 year of myo-/pericarditis diagnosis among individuals vaccinated with COMIRNATY as well as individuals not vaccinated with a COVID-19 vaccine.

In addition, a long-term primary data collection study is C4591036 (former Pediatric Heart Network (PHN), to evaluate the clinical course, risk factors, long-term sequelae, and quality of life of post-vaccine myocarditis/pericarditis over a 5-year period.

Finally, study C4591021 will also estimate the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.

Non-Interventional Post-Approval Safety Studies in Pregnancy

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 4 of the real-world safety studies (C4591009, C4591010, C4591011, and C4591021 [former ACCESS/VAC4EU]), described in Table 49. 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 49 and Table 50).

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 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 COVID-19 mRNA 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 COVID-19 mRNA vaccine following its introduction into the real-world setting.

Table 49. 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 imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2	Phase 1/2/3, randomised, 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-May-2021 31-Aug-2023
C4591009 US	A non-interventional post approval safety study Pfizer-BioNTech COVID-19 vaccine in the United States Non-Interventional *Planned*	To capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the Pfizer-BioNTech COVID-19 vaccine since its availability under an EUA using electronic health records and claims data from data partners participating in the Sentinel System.	Post-approval observational study using real-world data	The general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System	Protocol submission Monitoring report submission: Interim Analysis submission: Final study report submission	31 August 2021 31 October 2022 31 October 2023 31 October 2025

Table 49. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
C4591011 US	Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense population following Emergency Use Authorization Non-Interventional *Planned*	To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, including myocarditis and pericarditis following receipt of the COVID-19 mRNA vaccine.	Secondary use of real-world data to conduct comparative analyses using self-controlled risk interval and active comparator approaches	Department of Defense military and civilian personnel and their families in the Military Health System	Interim reports submission:	31-Dec-2021[7]
						30-Jun-2022
						31-Dec-2022
					Final CSR submission:	31-Dec-2023
C4591012 US	Post-Emergency Use Authorization active safety surveillance study among individuals in the Veteran's Affairs health system receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) vaccine Non-Interventional *Ongoing*	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the COVID-19 mRNA vaccine.	Secondary use of real-world data to conduct comparative analyses using self-controlled risk interval and active comparator approaches	US Veterans	Interim reports submission:	30-Jun-2021
						31-Dec-2021
						30-Jun-2022
						31-Dec-2022
					Final CSR submission:	31-Dec-2023
C4591010 EU	A Non-Interventional Post-Authorization Safety Study (PASS) for Active Safety Surveillance of recipients of the Pfizer-BioNTech COVID-19 mRNA vaccine in the EU	To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the	Primary data collection cohort study	EU general population	Final CSR submission:	30-Sep-2024

[7] PRAC agreed to remove the first milestone (Interim Report submission due 30 June 2021)

Table 49. Additional Pharmacovigilance Activities

Study Number ***Country (ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
	Non-Interventional *Planned*	COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates.				

Table 49. Additional Pharmacovigilance Activities

Study Number ***Country (ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
C4591015 Global	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 *Ongoing*	To assess safety and immunogenicity in pregnant women In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.	Randomised, placebo-controlled, observer-blind study	Healthy pregnant women 18 years of age or older vaccinated during their 24 to 34 weeks of gestation	Final CSR submission:	30-Apr-2023

Table 49. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
C4591014 US	Pfizer-BioNTech COVID-19 BNT162b2 vaccine effectiveness study - Kaiser Permanente Southern California Non-Interventional (Retrospective database analysis) *Planned*	To determine the effectiveness of COVID-19 mRNA vaccine when administered outside of the clinical setting. To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation 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	Final CSR submission:	30-Jun-2023
WI235284 US	Determining RSV burden and outcomes in pregnant women and older adults requiring hospitalization. COVID-19 Amendment for COVID VE / Sub-study 6 Low-Interventional[a] *Planned*	To determine the effectiveness of COVID-19 mRNA vaccine when administered outside of the clinical setting. To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation 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	Final CSR submission:	30-Jun-2023

Table 49. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
WI255886 Ex-EU[b]	Avon Community Acquired Pneumonia Surveillance Study. A pan-pandemic acute lower respiratory tract disease surveillance study Low-Interventional[a] *Planned*	To determine the effectiveness of COVID-19 mRNA vaccine when administered outside of the clinical setting. To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation 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	Final CSR submission:	30-Jun-2023
BNT162-01 Cohort 13 EU	Immunogenicity of Pfizer-BioNTech COVID-19 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:	30-Sep-2021
					Final CSR submission:	31-Dec-2022

Table 49. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	**Study Title** **Study Type** *Study Status*	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
C4591018 US	A phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 mRNA vaccine candidate against COVID-19 (BNT162b2) in adults with stable rheumatoid arthritis receiving background tofacitinib or background TNF inhibitors 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)	IA submission:	31-Dec-2021
C4591024 (former Safety and immunogenicity in high risk adults) Global	A Phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ⩾2 years of age Interventional *Planned*	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal disease).	Open uncontrolled	High risk individuals including frail, those having autoimmune disease, chronic renal disease and immunocompromising conditions	Final CSR submission:	31-Dec-2022

Table 49. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
C4591021 (former ACCESS/VAC4EU) EU	Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. Non-Interventional *Ongoing*	Assessment of potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis after being vaccinated with COVID-19 mRNA vaccine. Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.	Secondary database analysis of observational data to assess potential increased risk of adverse events of special interest (AESI and other clinically significant events among COVID-19 vaccine recipients in the EU.	General population	Final CSR submission:	30 Sep-2024[8]
C4591038 (former C4591021 substudy) EU	Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. Sub-study to	Assessment of the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious	Secondary database analysis of observational data	General population in EU: individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine	Final protocol submission	31 January 2022

[8] The start of the data collection will be 30 September 2021, with a progress report of the study which will be submitted 30 September 2021. Hereafter, 6-monthly interim reports till final study report 30 September 2024. This was accepted by PRAC in the Response Assessment Report for the Post-Authorisation Measure 017.1

Table 49. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
	investigate natural history of post-vaccination myocarditis and pericarditis Non-Interventional *Planned*	cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine			Final CSR submission:	30 September 2024
C4591036 (former Pediatric Heart Network Study) US	Safety surveillance study of myocarditis and myopericarditis temporally associated with Tozinameran (Comirnaty®) in persons < 21 years of age Non-Interventional *Planned*	To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis	Prospective cohort study	Patients <21 years presenting to PHN sites after receiving any dose of BNT162b2 and who were diagnosed with myocarditis / pericarditis as well as individuals not vaccinated with myocarditis/pericarditis	Protocol submission:	30-Nov-2021
					Final CSR submission:	31-Oct-2025
Co-administration study with seasonal influenza vaccine Not available	Co-administration of BNT162b2 with seasonal influenza vaccine. Interventional *Planned*	Safety and immunogenicity of COVID-19 mRNA vaccine and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Not available at this time.	General population	Protocol submission:	30-Sep-2021
					Final CSR submission:	31-Dec-2022

a. Case-control study nested in a prospective surveillance cohort, conducted as a research collaboration.
b. United Kingdom.

III.3. Summary Table of Additional Pharmacovigilance Activities

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

Table 50. 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 imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of 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 frail 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-May-2021
				Final CSR submission with supplemental follow-up:	31-Aug-2023

Table 50. 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					
C4591009 Planned	US	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, among individuals in the general US population and in subcohorts of interest within selected data sources participating in the US Sentinel System.	Myocarditis and pericarditis AESI-based safety events of interest Use in general population Use in pregnancy Use in immunocompromised patients Use in persons with a prior history of COVID-19	Protocol submission	31 August 2021
				Monitoring report submission	31 October 2022
				Interim Analysis submission:	31 October 2023
				Final study report submission:	31 October 2025
C4591011 *Planned*	US	To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine.	Myocarditis and pericarditis 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:	31-Dec-2021
					30-Jun-2022
					31-Dec-2022
				Final CSR submission:	31-Dec-2023
C4591012 *Ongoing*	US	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following	Myocarditis and pericarditis Anaphylaxis	Interim reports submission:	30-Jun-2021
					31-Dec-2021
					30-Jun-2022

Table 50. 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
		receipt of the COVID-19 mRNA vaccine.	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.		31-Dec-2022
				Final CSR submission:	31-Dec-2023

Table 50. 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	To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates.	Anaphylaxis AESI-based safety events of interest Use in pregnancy Long-term safety data.	Final CSR submission:	30-Sep-2024

Table 50. 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
C4591015 *Ongoing*	Global	To assess safety and immunogenicity in pregnant women In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.	Use in pregnancy and while breast feeding.	Final CSR submission:	30-Apr-2023
C4591014 *Planned*	US	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Final CSR submission:	30-Jun-2023
WI235284 *Planned*	US[a]	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Final CSR submission:	30-Jun-2023

Table 50. 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
WI255886 *Planned*	Ex-EU[a,b]	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Final CSR submission:	30-Jun-2023
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.	IA submission:	31-Dec-2021
C4591024 (former Safety and immunogenicity in high risk adults) *Planned*	Global	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal 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.	Protocol submission: Final CSR submission:	30-Jun-2021 31-Dec-2022

Table 50. 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
C4591021 (former ACCESS/VAC4EU) *Ongoing*	EU	Assessment of potential increased risk of adverse events of special interest (AESI) after being vaccinated with COVID-19 mRNA vaccine. Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.	Myocarditis and Pericarditis 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.	Final CSR submission:	30-Sep-2024
C4591038 (former C4591021 substudy) *Planned*	EU	To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine	Myocarditis and Pericarditis Long term safety data	Protocol submission:	31 January 2022
				Final CSR submission:	30 September 2024.
C4591036 (former Pediatric Heart Network Study)	US	To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young	Myocarditis and Pericarditis Long term safety data	Protocol submission:	30-Nov-2021

Table 50. 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**
Planned		adults <21 years with acute post-vaccine myocarditis		Final CSR submission:	31-Oct-2025
Co-administration study with seasonal influenza vaccine *Planned*	Not available	Safety and immunogenicity of COVID-19 mRNA vaccine 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. Case-control study nested in a prospective surveillance cohort, conducted as a research collaboration.
b. 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 51. 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.
Myocarditis and Pericarditis	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.

Table 51. Description of Routine Risk Minimisation Measures by Safety Concern

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 51. 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

The additional risk minimisation measure to address myocarditis and pericarditis is a Direct Healthcare professional communication, as below.

Table 52. Additional Risk Minimisation Measures for the Important Identified Risk of Myocarditis and Pericarditis

Direct Healthcare Professional Communication (DHPC)	
Objectives	To ensure that healthcare providers (HCPs) are aware of the potential for myocarditis and pericarditis associated with COVID-19 mRNA vaccine use.
Rationale for the additional risk minimisation activity:	The DHCP communication is to inform HCPs about the identified risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccine, to remind them to be alerted about the signs and symptoms and to counsel patients to seek immediate medical attention should they experience chest pain, shortness of breath, or palpitations
Target audience and planned distribution path:	The target audience includes general practitioners, cardiologists, specialists in emergency medicine and vaccination centres, HCPs who vaccinate patients and who provide medical care to patients who receive the vaccine. Target groups should be further defined at national level, depending on national health care systems
Plans to evaluate the effectiveness of the interventions and criteria for success:	Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination. The DHPC distribution started on 19 July 2021 in all EEA countries as per the EMA's communication plan.

V.3. Summary of Risk Minimisation Measures

Table 53. 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 (PART III.1 and Annex 4). Additional pharmacovigilance activities: Studies (Final CSR Due Date): • C4591001 (31-Aug-2023) • C4591009 (31-Oct-2025) • C4591010 (30-Sep-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024).

Table 53. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis and pericarditis	Routine risk minimisation measures: SmPC sections 4.4. and 4.8. Additional risk minimisation measures: DHCP letter and communication plan (see V.2 and Annex 6)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date): • C4591009 (31-Oct-2025) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) • C4591038 (former C4591021 substudy) (30-Sep-2024) • C4591036 [former Pediatric Heart Network study] (31-Oct-2025).
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 (PART III.1 and Annex 4). Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591001 (31-Aug-2023) • C4591009 (31-Oct-2025) • C4591011[b] (31-Dec-2023) • C4591012[b] (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) (30 Sep-2024)[b].

Table 53. 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](30-Sep-2024) • C4591009 (31-Oct-2025) • C4591011[a] (31-Dec-2023) • C4591015 (30-Apr-2023) • C4591021 (former ACCESS/VAC4EU)[a] (30-Sep-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) • C4591010[c] (30-Sep-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591018 (IA: 31-Dec-2021) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) • C4591024 (former Safety and immunogenicity in high risk adults) (31-Dec-2022)
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) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) • C4591024 (former Safety and immunogenicity in high risk adults) (31-Dec-2022)

Table 53. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) • C4591024 (former Safety and immunogenicity in high risk adults) (31-Dec-2022).
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 (30-Sep-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024). • C4591038 (former C4591021 substudy) (30-Sep-2024) • C4591036 (former PHN) (31-Oct-2025)

a. Please note that studies C4591009, C4591010, C4591011 and C4591021 (former ACCESS/VAC4EU) address only “Use in pregnancy”.
b. Addresses AESI-based safety events of interest including vaccine associated enhanced disease
c. Addresses AESI-based safety events of interest.

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 encapsulated 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 54. List of Important Risks and Missing Information

Important identified risks	Anaphylaxis Myocarditis and Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and 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 55. 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.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C4591001 • C4591009 • C4591010 • C4591011 • C4591012 • C4591021 (former ACCESS/VAC4EU) See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 56. Important Identified Risk: Myocarditis and Pericarditis

Evidence for linking the risk to the medicine	Events of Myocarditis and Pericarditis have been reported.
Risk factors and risk groups	Post-authorization reports have been reported more frequently in adolescent and young adult male patients following the second dose of vaccine; however, reports have been received for adult males and females of broader age range and following the first vaccination also.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4. and 4.8. Additional risk minimisation measures: Direct Healthcare Professional Communication (DHPC) letter and communication plan
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C4591009 • C4591011 • C4591012 • C4591021 (former ACCESS/VAC4EU) • C4591038 (former C4591021 sub-study) • C4591036 (former Pediatric Heart Network study) See Section II.C this summary for an overview of the post-authorisation development plan.

Table 57. 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 • C4591009[a] • C4591011[a] • C4591012[a] • C4591021 (former ACCESS/VAC4EU)[a] See Section II.C of this summary for an overview of the post-authorisation development plan.

a. Addresses AESI-based safety events of interest including vaccine associated enhanced disease

Table 58. 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: • C4591009[a] • C4591010[a] • C4591011[a] • C4591015 • C4591021 (former ACCESS/VAC4EU)[a] See Section II.C of this summary for an overview of the post-authorisation development plan.

a. Please note that studies C4591009, C4591010, C4591011 and C4591021 (former ACCESS/VAC4EU) address only "Use in pregnancy".

Table 59. 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 • C4591010[a] • C4591011 • C4591012 • C4591018 • C4591021 (former ACCESS/VAC4EU) • C4591024 (former Safety and Immunogenicity in high risk adults) See Section II.C of this summary for an overview of the post-authorisation development plan.

a. Addresses AESI-based safety events of interest

Table 60. 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 • C4591012 • C4591021 (former ACCESS/VAC4EU) • C4591024 (former Safety and immunogenicity in high risk adults) See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 61. 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 • C4591012 • C4591018 • C4591021 (former ACCESS/VAC4EU) • C4591024 (former Safety and immunogenicity in high risk adults) See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 62. 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 63. 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 • C4591021 (former ACCESS/VAC4EU) • C4591038 (former C4591021 substudy) • C4591036 (former PHN) 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 imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of 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
C4591009	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System.
C4591011	To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine.
C4591012	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine.
C4591010	To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates.

Study	Purpose of the study
C4591015	To assess safety and immunogenicity in pregnant women In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.
C4591014	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.
WI235284	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.
WI255886	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation 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; RA activity by Clinical Disease Activity Index; N-antigen antibodies for detection of asymptomatic infection.
C4591024 (former Safety and immunogenicity in high risk adults)	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal disease).
C4591021 (former ACCESS/VAC4EU)	Assessment of potential increased risk of adverse events of special interest (AESI) after being vaccinated with COVID-19 mRNA vaccine. Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.
C4591038 (former C4591021 substudy)	To assess the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine
C4591036 (former Pediatric Heart Network study)	To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis
Co-administration study with seasonal influenza vaccine	Safety and immunogenicity of COVID-19 mRNA vaccine 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 enable the retrieval of clinical details about potential anaphylactic reactions experienced by an individual following administration of Pfizer-BioNTech COVID-19 Vaccine.

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)	Time (24 hr)	Anatomical 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. Please describe all the signs and symptoms of the anaphylactic reaction [please also see Section 7]:
(Please include information on vital signs, e.g. blood pressure, oximetry)
Details:

2. Please describe the time course of the anaphylactic reaction:
(Please specify time of onset following vaccination, speed of progression and duration of signs and symptoms)
Details:

3. Did the patient require medical intervention?
☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (including dates and times of intervention)*
☐ *Adrenaline* ☐ *Corticosteroids* ☐ *Antihistamine* ☐ *IV fluids*
☐ *Oxygen* ☐ *Bronchodilators* ☐ *Other (please specify)*
Details:

4. Was/Is the patient seen in the Emergency Department?
☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

5. Was/Is the patient hospitalized?
☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., date of hospitalization and duration of stay)*
Details:

6. Was/Is the patient admitted to an Intensive Care Unit?
☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
(e.g., date of admission to ICU and duration of stay)
Details:

7. Please provide information on organ involvement

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

☐ Respiratory ☐ Cardiovascular ☐ Dermatological/Mucosal ☐ Gastrointestinal ☐ Other

Respiratory ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Bilateral wheeze/bronchospasm** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Stridor** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Upper airway swelling** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Respiratory distress** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details – specifically on the following:*
  - **Tachypnoea** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
  - **Increased use of accessory respiratory muscles** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
  - **Recession** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
  - **Cyanosis** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
  - **Grunting** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
- **Dry cough** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Hoarse voice ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Difficulty breathing (without wheeze or stridor) ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Sensation of throat closure ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Sneezing ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Rhinorrhea ☐ 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*
Measured hypotension ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Shock ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details – specifically on the following:*
Tachycardia ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Capillary refill time > 3 sec ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Reduced central pulse volume ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Decreased level of consciousness ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Loss of consciousness ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Other ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

Dermatological/Mucosal ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Generalized urticaria (hives) ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Generalized erythema ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Angioedema (not hereditary) ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g. local or generalized)*
Generalized pruritus with skin rash ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Generalized pruritus without skin rash ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Generalized prickle sensation ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Localized injection site urticaria ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Red and itchy eyes ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Other ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

Gastrointestinal ☐ 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*
Nausea ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Vomiting ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Other ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

ANY OTHER SYMPTOMS/SIGNS ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details

8. Did the event require the initiation of new medication or other treatment or procedure?

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

Details:

9. Patient's outcome following the potential anaphylactic reaction:

☐ 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:

10. 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	Date Performed (dd-Mmm-yyyy)	Results with units, if applicable	Reference Ranges, if applicable (or please state if abnormal or elevated/reduced)
☐ Mast cell tryptase			
☐ Immune markers (e.g. total IgE levels)			
☐ Complement activation test			
☐ Hematology			
☐ Clinical chemistry			
☐ Other relevant tests (please specify):_____			

Past Medical History Questions

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

11. Does the patient have a history of any previous allergies to specific products or any conditions indicative of an allergy?

☐ Medication *(please specify)*
☐ Vaccine *(please specify)*
☐ Foods *(please specify)*
☐ Environmental *(please specify)*
☐ Insect bite/sting *(please specify)*
☐ Latex *(please specify)*
☐ Chemical *(please specify)*
☐ Other *(please specify)*
☐ Asthma
☐ Arrythmia
☐ Urticaria
☐ Pruritus
☐ Mastocytosis
☐ Other *(please specify)*

Details:

12. If there is a previous history of any allergies, does the patient take (or have readily available) any specific medication related to this

☐ Adrenaline (Epipen) ☐ Corticosteroid ☐ Antihistamine ☐ Other

Details:

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

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

Details:

14. Did the patient receive any recent vaccines for any other conditions prior to the event being reported?

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

Details:

15. Did the patient receive any recent vaccines for SARS-CoV2 other than Pfizer-BioNTech COVID-19 Vaccine prior to the event being reported?

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

Details:

16. Has the patient received any other vaccines around the time of Pfizer-BioNTech COVID-19 Vaccine vaccination?

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

Details:

Revision History

Revision	Effective Date	Summary of Revisions
1.0	23-Dec-2020	New DCA

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
2.0	05-Jan-2021	Title updated to Pfizer-BioNTech COVID-19 Vaccine VAED
1.0	07-Dec-2020	New DCA