COMIRNATY (COVID-19 mRNA VACCINE)
RISK MANAGEMENT PLAN

RMP Version number: 5.0

Data lock point for this RMP: See below

Age group	Module SIII. Clinical Trial Exposure	Module SVII.3. Details of Important Risks
5 to <12 years of age	06 September 2021	06 September 2021 (Pfizer Clinical Database) 18 June 2021 (Pfizer Safety Database)
12-15 years of age	13 March 2021 (Pfizer Clinical Database)	30 September 2021 (Pfizer Safety Database, for both CT and non-CT datasets)
Booster in severely immunocompromised aged 12 -15 years of age	N/A	30 September 2021 (Pfizer Safety Database, non-CT dataset)
16 years and older	13 March 2021 (Pfizer Clinical Database) 23 October 2020 (BioNTech Clinical Database)	30 September 2021 (Pfizer Safety Database, for both CT and non-CT datasets)
Booster in 16 years and older [a], including immunocompromised	17 June 2021 (Pfizer Clinical Database)	30 September 2021 (Pfizer Safety Database, for both CT and non-CT datasets)
Post-Authorisation Experience: 30 September 2021		

a. The safety and immunogenicity of a booster dose (third dose) of Comirnaty in individuals 65 years of age and older is based on safety and immunogenicity data in adults 18 to 55 years of age.

Date of final sign off: 02 February 2022

Rationale for submitting an updated RMP (v 5.0): EU-RMP v 2.6 was submitted in procedure EMEA/H/C/005735/II/0087 to update the RMP following the outcome of procedure EMEA/H/C/005735/II/0062 (third dose in immunocompromised individuals) and procedure 87 EMEA/H/C/005735/II/0067 (booster dose). The purpose of the update of RMP version 2.6 is to address the Requests for Supplementary Information received on 04 January 2022 with the PRAC Rapporteur's preliminary AR EMEA/H/C/005735/II/0087. As agreed via email on 12 January 2022 the requested changes are implemented in a consolidated version based on the currently effective RMP v 4.0.

Summary of significant changes in this RMP:

RMP Part/Module	Major Change (s)
PART I PRODUCT(S) OVERVIEW	Addition of booster dose.
PART II SAFETY SPECIFICATION	
PART II.Module SI Epidemiology of the Indication(s) and Target Populations	No changes made.
PART II.Module SII Non-Clinical Part of the Safety Specification	No changes made.
PART II.Module SIII Clinical Trial Exposure	Addition of text and exposure tables from Study C4591001 Phase 3 participants 18 to 55 years who received the BNT162b2 booster dose. Addition of final enrolment numbers of study C4591015.
PART II.Module SIV Populations Not Studied in Clinical Trials	Addition of text for booster dose group in SIV.3.
PART II.Module SV Post-Authorisation Experience	Updated with new DLP 30 September 2021.
PART II.Module SVI Additional EU Requirements for the Safety Specification	No changes made.
PART II.Module SVII Identified and Potential Risks	Addition of data related to booster dose group for the important risks of anaphylaxis, myocarditis and pericarditis and VAED/VAERD and DLP revised as per table above.
PART II.Module SVIII Summary of the Safety Concerns	No changes made.
PART III PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	
III.1 Routine Pharmacovigilance activities	Inclusion of the new DCA for MIS/C and MIS/A.
III.2 Additional Pharmacovigilance Activities and III.3 Summary Table of Additional Pharmacovigilance Activities	Inclusion of booster dose analyses/milestones for the following non interventional studies: C4591009, C4591012, C4591010, C4591011, C4591021, C4591036 and C4591038; Addition of NIS C4591022.
PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES	No changes made.
PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	

RMP Part/Module	Major Change (s)
V.1 Routine Risk Minimisation Measures	Updated to reflect the preparation of bi-monthly summary safety reports
V.2 Additional Risk Minimisation Measures	
V.3 Summary of Risk Minimisation Measures	Updated based on the changes made in PART III
PART VI SUMMARY OF THE RISK MANAGEMENT PLAN	
I The Medicine and What It Is Used For	No changes made.
II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks	
PART VII ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 2: Studies/milestones updated Annex 3: Studies updated Annex 4: DCA for MIS/C and MIS/A Annex 7: Booster dose card included Annex 8: Changes to reflect the updates

Other RMP versions under evaluation:

Not applicable.

Details of the currently approved RMP

- RMP version number: 4.0

Approved with (combined) procedure number: EMEA/H/C/005735/X/0077

Date of approval: 26 November 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
ALC-0315	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
ALC-0159	2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
ARDS	acute respiratory distress syndrome
BALB/c	bagg albino
BC	Brighton Collaboration
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

Abbreviation	Definition of Term
IFN	interferon
IL-4	interleukin 4
IM	intramuscular(ly)
IMD	index of multiple deprivation
IND	investigational new drug
LNP	lipid nanoparticle
MAH	marketing authorisation holder
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
NHLBI	National Heart, Lung and Blood Institute
NHP	nonhuman primate
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIS	Non interventional study
NSCLC	non-small-cell lung carcinoma
OCS	oral corticosteroids
PASS	post-authorisation safety study
PC	product complaint
PK	pharmacokinetic
PHN	Pediatric Heart Network
PRAC	Pharmacovigilance risk assessment committee
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

Abbreviation	Definition of Term
UK	United Kingdom
US	United States
V8	variant 8
V9	variant 9
VAC4EU	Vaccine monitoring Collaboration for Europe
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
WBC	white blood cells
WHO	World Health Organisation
WOCBP	women of child-bearing potential

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Tozinameran 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 Comirnaty: – is nucleoside-modified messenger RNA formulated in LNPs; – is a white to off-white frozen dispersion (pH:6.9 – 7.9). - Excipients for 30 micrograms/dose concentrate for dispersion for injection (PBS-Sucrose): • ((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.

	- Excipients for 30 micrograms/dose dispersion for injection (Tris-Sucrose): • ALC-0315 • ALC-0159 • DSPC • cholesterol • trometamol • trometamol hydrochloride • sucrose • water for injections. - Excipients for 10 micrograms/dose concentrate for dispersion for injection, Children 5 to 11 years (Tris-sucrose): • ALC-0315 • ALC-0159 • DSPC • cholesterol • trometamol • trometamol hydrochloride sucrose • water for injections The Tris-sucrose formulation is based on the current approved vaccine except that the formulation buffer has been changed from phosphate buffered saline to Tris buffer without sodium chloride and potassium chloride while maintaining the same target pH.
Hyperlink to the Product Information:	Please refer to Module 1.3.1 of this submission
Indication in the EEA	Current: Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 5 years of age and older.

Dosage in the EEA	**Current PBS-Sucrose** *Individuals 12 years of age and older:* 30 micrograms/dose concentrate for dispersion for injection is administered intramuscularly after dilution as a course of 2 doses (0.3 mL each). It is recommended to administer the second dose 3 weeks after the first dose. A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older. The decision when and for whom to implement a third dose of Comirnaty should be made based on available vaccine effectiveness data, taking into account limited safety data. *Severely immunocompromised aged 12 years and older* A third dose may be given at least 28 days after the second dose to individuals who are severely immunocompromised. *Elderly* The safety and immunogenicity of a booster dose (third dose) of Comirnaty in individuals 65 years of age and older is based on safety and immunogenicity data in adults 18 to 55 years of age. **Current Tris-sucrose** *Individuals 12 years of age and older:* 30 micrograms/dose dispersion for injection is administered intramuscularly as a course of 2 doses (0.3 mL each) at least 21 days apart. Children 5 to 11 years: 10 micrograms/dose concentrate for dispersion for injection is administered intramuscularly after dilution as a course of 2 doses (0.2 mL each). It is recommended to administer the second dose 3 weeks after the first dose.
Pharmaceutical form and strengths	**Current PBS-Sucrose** *Individuals 12 years of age and older:* 30 micrograms/dose concentrate for dispersion for injection (Purple cap). After dilution each vial contains 6 doses of 0.3 mL **Current Tris-sucrose** *Individuals 12 years of age and older:* 30 micrograms/dose dispersion for injection (Grey cap): One vial (2.25 mL) contains 6 doses of 0.3 mL. The drug product does not require dilution for administration. Children 5 to 11 years: 10 micrograms/dose concentrate for dispersion for injection (Orange cap). After dilution each vial contains 10 doses of 0.2 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 5 years of age and older.

Incidence:

The coronavirus disease of 2019 (COVID-19) is caused by a novel coronavirus labelled as SARS-CoV-2. The disease first emerged in December 2019, when a cluster of patients with pneumonia of unknown cause was recognised in Wuhan City, Hubei Province, China.[1] The number of infected cases rapidly increased and spread beyond China throughout the world. On 30 January 2020, the WHO declared COVID-19 a Public Health Emergency of International Concern and thus a pandemic.[2]

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

As of 15 August 2021, the overall number of people who had been infected with SARS-CoV-2 was over 207 million worldwide[4], an increase of 92 million in the 5 months since 03 March 2021[5]. Table 1 shows the incidence and prevalence as of 15 August 2021 for the US, UK, and EU-27 countries. In the EU and the UK, by 15 August 2021 the total number of confirmed cases had accumulated to 41 million people, or 8,074 per 100,000 people (from 27 million, or 5,226 per 100,000 by 03 March 2021). Across countries in the EU, the number of confirmed cases ranged from 2,118 to 15,620 cases per 100,000 people. Finland and Germany 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 37 million cases (11,236 per 100,000 people) by 15 August 2021.[4] This is an increase from 29 million (8,864 per 100,000) by 03 March 2021.[5]

Table 1. Incidence, Prevalence, and Mortality of COVID-19 as of 15 August 2021[4]

	Total Cases	Incidence: Total Cases/100,000	Active Cases	Prevalence: Active Cases/ 100,000	Total Deaths	Mortality: Deaths / 100,000	Population
Global	207,731,370	2,665	17,141,537	220	4,371,692	56	7,794,798,124
EU-27	35,243,565	7,910	2,000,178	449	747,450	168	445,541,383
UK	6,241,011	9,140	1,313,343	1,923	130,894	192	68,284,715
EU-27 + UK	41,484,576	8,074	3,313,521	645	878,344	171	513,826,098
US	37,435,835	11,236	6,653,787	1,997	637,439	191	333,172,543
EU-27 Countries							
Austria	668,732	7,378	8,559	94	10,756	119	9,063,848
Belgium	1,149,869	9,873	52,835	454	25,287	217	11,646,025
Bulgaria	432,962	6,284	14,645	213	18,339	266	6,889,852
Croatia	367,022	9,002	1,903	47	8,283	203	4,076,913
Cyprus	108,707	8,931	17,496	1,437	456	38	1,217,182
Czech Republic	1,676,222	15,620	2,441	23	30,373	283	10,731,206
Denmark	330,777	5,688	12,854	221	2,560	44	5,815,014
Estonia	136,992	10,319	5,131	387	1,279	96	1,327,533
Finland	117,531	2,118	70,536	1,271	995	18	5,550,349
France	6,449,863	9,857	455,926	697	112,612	172	65,435,079
Germany	3,825,039	4,549	53,169	63	92,370	110	84,083,573
Greece	535,237	5,163	37,611	363	13,174	127	10,366,043
Hungary	810,316	8,412	14,326	149	30,038	312	9,632,892
Ireland	322,989	6,461	42,205	844	5,059	101	4,999,386
Italy	4,435,008	7,347	126,466	210	128,413	213	60,362,319
Latvia	140,122	7,522	1,218	65	2,561	138	1,862,827
Lithuania	289,810	10,815	12,355	461	4,451	166	2,679,705
Luxembourg	74,595	11,704	705	111	828	130	637,340
Malta	35,337	7,979	1,043	236	430	97	442,858
Netherlands	1,901,900	11,072	124,498	725	17,909	104	17,177,282
Poland	2,885,333	7,633	154,721	409	75,299	199	37,800,220
Portugal	1,003,335	9,872	45,367	446	17,562	173	10,163,426
Romania	1,087,223	5,694	2,982	16	34,348	180	19,093,951
Slovakia	393,529	7,204	825	15	12,544	230	5,462,601
Slovenia	261,428	12,573	2,150	103	4,433	213	2,079,258
Spain	4,693,540	10,034	722,353	1,544	82,470	176	46,775,041
Sweden	1,110,147	10,916	15,858	156	14,621	144	10,169,660

The reported numbers refer to cases that have been tested and confirmed to be carrying the virus and sometimes, depending upon the country, also presumptive, suspect, or probable cases of detected infection. 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.[6]

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 15 August 2021, the overall prevalence estimates for the EU and UK were 449 and 1,923 active cases per 100,000, respectively, [4] compared to approximately 1,500 per 100,000 for both the EU and UK on 03 March 2021[5]. The range of reported prevalence was 15 to 1,544 per 100,000: Slovakia, Romania, and Czech Republic reported the lowest prevalence while Spain, Cyprus, and Finland reported the highest (Table 1).

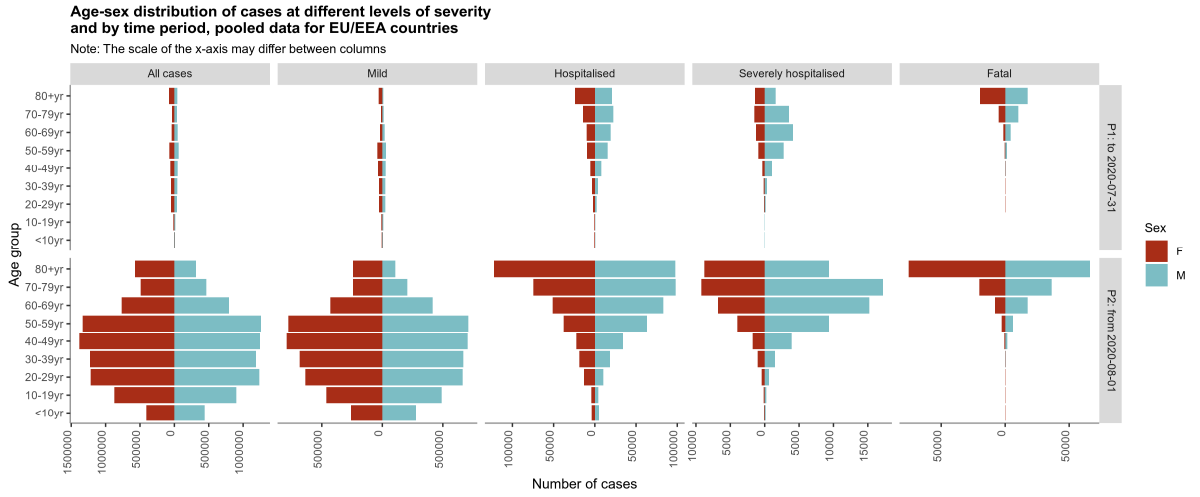
In the US, the prevalence on 15 August 2021 was similar to UK 1,997 active cases per 100,000[4]. This is a decrease of approximately 700 per 100,000 since 03 March 2021, when the prevalence was 2,685 per 100,000[5].

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 EU/EEA member states. 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 12 August 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 08 August 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-Sex distribution of COVID-19 Cases as Different Levels of Severity, Pooled data for EU/EEA countries. Case-based Data from TESSy produced on 12 August 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 31, 2021. 12 August 2021. "2.2 Age-sex pyramids" Accessed 15 August 2021.

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 as of 14 August 2021[9]. At that time, the CDC reported that the US had recorded a total of 36,556,516 cases of COVID and 618,591 deaths attributable to the disease. However, because demographic data were not available for all US COVID cases and deaths, the numbers in Table 2 and Table 3 are drawn, respectively, from 29,346,352 cases and 513,204 deaths. Those under age 50 account for 67% of all cases but approximately for only 5% of deaths. For ages 18-74, males account for less than half of cases but over 60% of deaths. Among the paediatric population, there is close to a 50-50 case distribution between males and females across ages 0-17. However, the paediatric mortality distribution is highly irregular between the sexes, with males being 51.5% of COVID deaths among 0-4-year-old, 55.9% among 5-11-year-old, 46.7% among 12–15-year-old, and 68.7% among 16-17-year-old.

Table 2. Distribution of Cases (n=29,346,352) by Age, Sex, Race, and Cross-Tabulated Age and Sex - United States[9] as of 14 August 2021[a]

Event	Age Group	Age %	Sex	Sex %	Race[b]	Race %	Age Group	Males %	Females %
Cases	**0-4**	2.2	**Males**	47.7	**H/L**	28.3	**0-4**	51.7	48.3
	5-11	4.2	**Females**	52.3	**AI/AN**	1	**5-11**	50.8	49.1
	12-15	3.8			**Asian**	3.2	**12-15**	49.6	50.4
	16-17	2.6			**Black**	11.6	**16-17**	48.3	51.7
	18-29	22.7			**NH/PI**	0.3	**18-29**	46.9	53.1
	30-39	16.6			**White**	50.3	**30-39**	47.9	52.1
	40-49	14.8			**M/O**	5.3	**40-49**	47.7	52.3
	50-64	20					**50-64**	48.6	51.4
	65-74	7.3					**65-74**	48.7	51.3
	75-84	3.7					**75-84**	45.7	54.3
	85+	2.1					**85+**	34.4	65.6

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

Table 3. Distribution of Deaths (n=513,204) by Age, Sex, Race, and Cross-Tabulated Age and Sex - United States[9] as of 14 August 2021[a]

Event	Age Group	Age %	Sex	Sex %	Race[b]	Race %	Age Group	Males %	Females %
Deaths	0-4	<0.1	Males	54.2	H/L	18.5	0-4	51.5	48.5
	5-11	<0.1	Females	45.8	AI/AN	1.2	5-11	55.9	44.1
	12-15	<0.1			Asian	3.8	12-15	46.7	53.3
	16-17	<0.1			Black	13.8	16-17	68.7	31.3
	18-29	0.6			NH/PI	0.2	18-29	64	36
	30-39	1.3			White	58.7	30-39	65.1	34.9
	40-49	3.1			M/O	3.8	40-49	65.3	34.7
	50-64	15.4					50-64	64	36
	65-74	21.6					65-74	60.6	39.4
	75-84	27.3					75-84	55.5	44.5
	85+	30.7					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.

The most recent CDC estimate of the total number of excess deaths (as opposed to overall deaths in the preceding paragraph) across the US from 26 January 2020 to 27 February 2021 from all causes (COVID-19 and otherwise) ranged from 545,600 - 660,200, with an estimated 75-88% of excess deaths being associated with COVID-19.[19] An earlier CDC report on excess deaths covering 26 January 2020 through 3 October 2020 broke down excess deaths by demographics[20]: by age during that period, 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.

While research earlier in the pandemic tended to focus on adults, more recent data have given greater attention to children and adolescents. For the period January 1- March 31, 2021 across 14 states (the most recently available data), the CDC's COVID-NET database recorded 204 adolescents aged 12-17 who were hospitalized for likely primarily COVID-19-related reasons.[21] The 204 adolescents were 47.5% male—consistent with the COVID case sex distribution across all ages—and disproportionately from minorities, with 31.4% Hispanic and 35.8% non-Hispanic African Americans.[21]

Another recent CDC report described demographic trends in US COVID-19 incidence among 15,068 cases aged 0-24 years across 16 jurisdictions during the period 01 January 2020 through 31 December 2020.[22] The report broke down incidence by age groups and 2020 sub-periods that are presented in Table 4. The table shows that early in 2020, 5-9-year-old were experiencing less COVID-19 than 0-4-year-old, but by the end of the year this pattern had reversed. Compared to 5-9-year-old, the age categories 10-14, 15-19, and 20-24 years old showed progressively greater incidence rates, a pattern that held throughout 2020.

Table 4. COVID-19 incidence and rate ratios, by age group among persons aged <25 years across three periods of 2020 in 16 U.S. jurisdictions [22]

2020 Sub-Period	Age Group (years)	Number of Cases	Cases per 100,000 population (95% CI)	Rate Ratio (95% CI)
Jan 1 - Apr 30	0-4	956	21 (20-23)	1.28 (1.17-1.41)
	5-9	772	17 (16-18)	Reference
	10-14	1,184	25 (23-26)	1.49 (1.36-1.63)
	15-19	3,267	67 (65-70)	4.03 (3.72-4.36)
	20-24	8,889	175 (171-178)	10.47 (9.72-11.26)
May 1 - Aug 31	0-4	14,017	314 (309-319)	1.01 (0.98–1.03)
	5-9	14,406	312 (307-317)	Reference
	10-14	20,490	430 (424-436)	1.38 (1.35–1.41)
	15-19	50,210	1,034 (1,025-1,043)	3.32 (3.26–3.38)
	20-24	78,655	1,547 (1,536-1,557)	4.96 (4.88–5.05)
Sep 1 - Dec 31	0-4	33,595	752 (744–760)	0.71 (0.70–0.72)
	5-9	48,824	1,056 (1,047–1,066)	Reference
	10-14	76,922	1,615 (1,604–1,627)	1.53 (1.51–1.55)
	15-19	149,660	3,083 (3,067–3,098)	2.92 (2.89–2.95)
	20-24	187,825	3,693 (3,677–3,710)	3.50 (3.46–3.53)

Other US paediatric data are generally consistent with the CDC findings. Table 5 summarizes demographic results for a retrospective cohort of 135,794 individuals under the age of 25 who were tested for COVID-19 by 08 September 2020 within the PEDSnet network of US paediatric health systems.[23] The table shows that, among the paediatric population, children age 12-17 were more frequently infected than those under age 12. African Americans and Hispanics had elevated frequencies of testing positive relative to their proportion of the cohort.

A study of 1,945,831 individuals aged 0-18 recorded in the Premier Healthcare Database between March and October 2020 included 20,714 paediatric cases of COVID-19; the authors reported similar patterns to what is shown in Table 4, with the additional observation that COVID-19 cases aged 0-1 and 12-18 years were more likely to develop serious illness than those aged 2-11.[24]

Table 5. Demographics of 135,794 US individuals under age 25 tested for COVID-19 by 08 September 2020[23]

Characteristic	Patients, n (%)		
	COVID-19 negative (n=130,420)	COVID-19 positive, Asymptomatic or mild illness (n=5,015)	COVID-19 positive, Severe illness (n=359)
Age, years			
<1	17,431 (13)	494 (10)	72 (20)
1-4	32,619 (25)	808 (16)	40 (11)
5-11	35,617 (27)	1,029 (21)	72 (20)
12-17	32,362 (25)	1,521 (30)	117 (33)
18-24	12,391 (10)	1,163 (23)	58 (16)
Sex			
Female	61,637 (47)	2,527 (50)	172 (48)
Male	68,701 (53)	2,485 (50)	187 (52)
Other or Unknown	82 (0.06)	3 (0.06)	0
Race/ethnicity			
Hispanic	14,156 (11)	918 (18)	108 (30)
API	4,471 (3)	151 (3)	9 (3)
Black or AA	18,646 (14)	1,424 (28)	119 (33)
White	77,540 (60)	1,988 (40)	97 (27)
Multiple	3,883 (3)	126 (3)	5 (1)
Other or Unknown	11,724 (9)	408 (8)	21 (6)

AA=African American, API=Asian or Pacific Islander

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.[25] 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.[25,26] Among children, the primary source of infection is an infected adult living in the same household.[27] According to the CDC, some ethnic minority groups have a higher risk of infection, but age is not associated with risk of initial infection among people aged 5 and older (Table 6).[28,29]

Table 6. Risk for COVID-19 Infection, Hospitalisation, and Death by Age Group and by Race/Ethnicity[29]

		Rate ratios[c]	
Age Group (years)	**Cases[d]**	**Hospitalisation[e]**	**Death[f]**
0-4	<1	<1	<1
5-17[a]	1	<1	<1
18-29	1	1	1
30-39	1	2	4
40-49	1	2	10
50-64	1	4	35
65-74	1	6	95
75-84	1	9	230
85+	1	15	600
Race/Ethnicity			
Non-Hispanic White[b]	1	1	1
American Indian or Alaska Native, non-Hispanic	1.7	3.4	2.4
Asian, non-Hispanic	0.7	1.0	1.0
Black or African American, non-Hispanic	1.1	2.8	2.0
Hispanic or Latino	1.9	2.8	2.3

a. Rate ratios for each age group are relative to the 18-29-year age category. This group was selected as the reference group because it has accounted for the largest cumulative number of COVID-19 cases compared to other age groups.
b. Rate ratios for each race/ethnicity group are relative to the Non-Hispanic White category.
c. Rates are expressed as whole numbers, with values less than 10 rounded to the nearest integer, two-digit numbers rounded to nearest multiple of five, and numbers greater than 100 rounded to two significant digits.
d. Includes all cases reported by state and territorial jurisdictions (accessed on July 12, 2021). The denominators used to calculate rates were based on the 2019 Vintage population (https://www.census.gov/newsroom/press-releases/2019/popest-nation.html).
e. Includes all hospitalizations reported through COVID-NET (from March 1, 2020 through July 3, 2021, accessed on July 12, 2021). Rates were standardized to the 2020 US standard COVID-NET catchment population (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html).
f. Includes all deaths in National Center for Health Statistics (NCHS) provisional death counts (accessed on July 12, 2021). The denominators used to calculate rates were based on the 2019 Vintage population (https://data.cdc.gov/NCHS/Provisional-COVID-19-Deaths-by-Sex-and-Age/9bhg-hcku).

Risk for severe or fatal COVID-19 disease has been shown to increase with older age, male sex, or ethnic minority status.[30 29 29 31 32 33] Children aged 5-17 typically experience a milder disease course and have lower risk of hospitalization or death.[28 34 35] Among adults, these risks increase for every 10-year age group above age 39 (Table 3).[28 36] Table 6 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 = 3.4 for hospitalisation and 2.4 for death) and Hispanic or Latino persons (RR = 2.8 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.[29]

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. [31] [32] [36] 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; people with developmental, behavioural or substance abuse disorders; and newly resettled refugee populations.[37]

Among adults, risk for severe or fatal COVID-19 disease increases with the presence of chronic medical conditions, including obesity, chronic lung 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, immunosuppression, HIV higher scores on the WHO Clinical Progression Scale and Charlson Comorbidity Index. [31] [32] [36] [38] Table 7 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 (with 17,000 COVID-19-related deaths) in England. [36]

The presence of one or more underlying medical conditions also increases risk of severe or fatal disease among children aged 5-17. [39] [40] [41] [42] In particular, childhood obesity has been consistently associated with two to three times the risk of severe disease or hospitalization. [39] [42] [43] [44] For many other individual comorbid conditions, paediatric sample sizes are very small and different studies produce conflicting results, so it is difficult to estimate precise risk ratios based on current literature. [27] [41]

Table 7. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death [36]

Characteristic	Category	COVID-19 death Hazard Ratio	
		Adjusted for age, sex, and NHS administrative region	Fully adjusted
Age	18-39	0.05 (0.04-0.06)	0.06 (0.04-0.07)
	40-49	0.32 (0.28-0.38)	0.34 (0.29-0.39)
	50-59	1.00 (ref)	1.00 (ref)
	60-69	2.93 (2.69-3.20)	2.57 (2.35-2.80)
	70-79	9.17 (8.48-9.93)	6.74 (6.21-7.31)
	80+	43.16 (40.03-46.53)	24.10 (22.23-26.13)
Sex	Female	1.00 (ref)	1.00 (ref)
	Male	1.73 (1.68-1.78)	1.55 (1.50-1.60)
BMI (kg/m^2)	Not obese	1.00 (ref)	1.00 (ref)
	30-34.9 (obese class I)	1.23 (1.18-1.28)	1.07 (1.03-1.12)
	35-39.9 (obese class II)	1.79 (1.68-1.90)	1.44 (1.36-1.54)
	40+ (obese class III)	2.76 (2.54-3.00)	2.11 (1.93-2.29)
Smoking	Never	1.00 (ref)	1.00 (ref)
	Former	1.44 (1.40-1.49)	1.26 (1.22-1.30)
	Current	1.17 (1.10-1.25)	0.97 (0.91-1.04)
Ethnicity	White	1.00 (ref)	1.00 (ref)
	Mixed	1.59 (1.28-1.97)	1.43 (1.15-1.78)
	South Asian	1.97 (1.82-2.14)	1.70 (1.55-1.85)
	Black	1.82 (1.61-2.05)	1.44 (1.27-1.63)
	Other	1.38 (1.17-1.63)	1.38 (1.16-1.63)
IMD quintile[a]	1 (least deprived)	1.00 (ref)	1.00 (ref)
	2	1.17 (1.11-1.23)	1.13 (1.07-1.19)
	3	1.37 (1.30-1.44)	1.25 (1.19-1.32)
	4	1.77 (1.68-1.86)	1.53 (1.46-1.61)
	5 (most deprived)	2.11 (2.01-2.22)	1.71 (1.62-1.80)
Blood pressure	Normal	1.00 (ref)	1.00 (ref)
	High BP or diagnosed hypertension	1.09 (1.06-1.13)	0.90 (0.87-0.94)
Respiratory disease excluding asthma		1.95 (1.86–2.04)	1.66 (1.59-1.73)
Asthma (vs. none)	With no recent OCS use	1.15 (1.10-1.21)	1.00 (0.95-1.05)
	With recent OCS use	1.61 (1.47-1.75)	1.15 (1.05-1.26)
Chronic heart disease		1.57 (1.51–1.64)	
Diabetes[b] (vs. none)	With HbA1c < 58 mmol/mol	1.53 (1.47-1.59)	1.20 (1.16-1.25)
	With HbA1c ≥ 58 mmol/mol	2.57 (2.45-2.70)	1.83 (1.74-1.93)
	With no recent HbA1c measure	2.19 (2.02-2.37)	1.71 (1.58-1.86)
Cancer (non-hematological, vs. none)	Diagnosed <1 year ago	1.47 (1.31-1.65)	1.44 (1.28-1.62)
	Diagnosed 1-4.9 years ago	1.13 (1.04-1.22)	1.11 (1.03-1.20)

Table 7. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death [36]

Characteristic	Category	COVID-19 death Hazard Ratio	
		Adjusted for age, sex, and NHS administrative region	Fully adjusted
	Diagnosed ≥ 5 years ago	0.99 (0.95-1.04)	2.41 (1.86-3.13)
Hematological malignancy (vs. none)	Diagnosed <1 year ago	2.54 (1.96-3.29)	2.80 (2.08–3.78)
	Diagnosed 1-4.9 years ago	2.28 (1.95-2.66)	2.25 (1.92-2.62)
	Diagnosed ≥ 5 years ago	1.71 (1.51-1.93)	1.65 (1.46-1.87)
Reduced kidney function[c] (vs. none)	eGFR 30-60	1.50 (1.45-1.55)	1.30 (1.25-1.35)
	eGFR 15-< 30	2.74 (2.56-2.93)	2.52 (2.33–2.72)
	eGFR <15 or dialysis	6.40 (5.75-7.12)	4.42 (3.93-4.98)
Liver disease		2.27 (2.01-2.57)	1.75 (1.54-1.98)
Dementia		4.59 (4.33-4.87)	3.62 (3.41-3.84)
Stroke		2.03 (1.95-2.12)	1.53 (1.46-1.59)
Other neurological disease		3.15 (2.96-3.36)	2.72 (2.55-2.90)
Organ transplant		5.54 (4.51-6.81)	1.61 (1.28-2.02)
Asplenia		1.50 (1.16-1.95)	1.26 (0.97-1.64)
Rheumatoid arthritis, lupus, or psoriasis		1.30 (1.21–1.38)	1.23 (1.17-1.30)
Other immunosuppressive condition		2.75 (2.10–3.62)	2.00 (1.57-2.54)

a. Classification by HbA1c is based on the most recent measurement within 15 months of baseline.
b. eGFR is measured in ml min−1 per 1.73 m2 and derived from the most recent serum creatinine measurement.
c. Index of Multiple Deprivation (derived from the patient's postcode)
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), AstraZeneca (EU/1/21/1529) and Janssen (EU/1/20/1525). 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- 45 %, across age groups[45 46 47 48] to critical illness and death. The rate of asymptomatic infection decreases with increasing age and long-term care facilities are associated with a lower rate of asymptomatic infection when compared to household transmission or other healthcare facilities. [48] A recent meta-analysis has estimated that 46.7% of infections in children are asymptomatic. [48] The most common symptoms of COVID-19 are fever, cough, and shortness of breath for both children and adults (Table 8).[49 50]

Table 8. 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

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

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

Progression and Timeline of Mild to Moderate Disease

Mild to moderate disease is defined as the absence of viral pneumonia and hypoxia. For those who develop symptoms, the incubation period is usually 4 to 5 days, with 97.5% experiencing symptoms within 11 days of exposure.[51] [52] 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.[52] Data on rates of re-infection are limited but variants may lead to increased risk of re-infection in the future. [51]

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 05 September 2021, there were 2,816,280 new hospital admissions for patients with confirmed COVID-19 in the US.[53] For the week ending 22 August 2021, 3.5 patients per 100,000 population were hospitalised due to COVID-19 in 21 countries of the EU/EEA with available data.[54] Based on data from 23 states and New York City, as of August 19, 2021, 1.6%-3.6% of children with COVID-19 have been hospitalised and 0.0-0.03% of children with COVID-19 have died.[55]

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 diarrhoea (33%).[56] [57] [58] [59]

COVID-19 patients also commonly experience gustatory disorders (44%) and olfactory disorders (53%).[60] Among non-hospitalised children < 18 years of age, 89% experienced one or more typical symptoms of COVID, including fever, cough, shortness of breath, and 22% experienced all three. [57] Approximately 17% to 40% of those hospitalised with COVID-19 experience severe symptoms necessitating intensive care [11 16 56] with 31% of children hospitalised experiencing severe COVID-19 that necessitates intensive care or invasive ventilation or ends in death. Risk factors for severe COVID-19 in hospitalised children include presence of a comorbid condition, younger age, and male sex.[61] More than 75% of patients hospitalised with COVID-19 require supplemental oxygen.[62]

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.[51] 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.[63] A 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. [46]

Mortality

As of 17 August 2021, there were 620,493 deaths reported in the US for all age groups among 36,951,181 cases (1.7% of cases).[64] As of 17 August 2021 there were 746,566 deaths reported for all age groups in the EU/EEA among 35,381,520 cases (2.1% of cases).[65] As of 17 August 2021, the UK has seen 131,466 deaths from COVID-19 in all age groups among 6,352,224 cases (2.1% of cases).[66] According to a recent meta-analysis of paediatric studies published through October 2020, the mortality for paediatric patients 0.1-2%.[67 46] In a study from January through June 2020 using the National Child Mortality Database (NCMD) in England, 5.7% of 437 children 0-17 years of age who died were SARS-CoV-2 PCR-positive and those who died of COVID-19 were older and were more likely to be non-White ethnicity.[68]

Mortality data are also presented from Worldometer, an independent organisation that publishes current, reliable COVID-19 statistics online.[3] The mortality of SARS-CoV-2 infection is defined as the cumulative number of deaths among detected cases.

As of 15 August 2021, the overall SARS-CoV-2 mortality for the EU + UK was 878,344 deaths, or 171 per 100,000 people. Reported mortality among EU countries and the UK ranged from 18 to 312 deaths per 100,000 (Table 1). Finland and Cyprus reported the lowest mortality; Hungary, Czech Republic, and Bulgaria reported the highest.[4]

In the US, as of 15 August 2021, the mortality was 637,439 deaths (191 per 100,000 people). Mortality in the US was very similar to that of UK (192 per 100,000).

Overall reported mortality among hospitalised COVID-19 patients varies from 12.8% to 26% in the EU, US and UK. [16,18,69,70] Mortality rates are declining over time, presumably due to an improved understanding of COVID-19 and its management.[71]

Complications of COVID-19 and Long-COVID

Complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney, and coagulation system.[11,14,72] 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.[73]

COVID-19 symptoms can persist weeks or months beyond the acute infection.[74,75] 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).[76]

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%).[77] Post-acute COVID symptoms in children with asymptomatic or mild disease appear to be less severe than in adults, with the most common symptoms being a post-viral cough (4%), fatigue (2%), or both symptoms (1%) with the duration of symptoms lasting 3 to 8 weeks[78].

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.[46 79, 80] As of August 19, 2021 there were 4,403 cases of MIS-C reported to health departments in the United States.[81]. Additional symptoms of MIS-C include abdominal pain, bloodshot eyes, chest tightness or pain, diarrhoea, lethargy, headache, low blood pressure, neck pain, and vomiting.[82]

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 56 59] 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 9 using TESSy data posted on 12 August 2021[83] below.

Table 9. Preconditions among COVID-19 Patients in EU/EEA, by Severity of Disease. Case-based Data from TESSy Reported 12 August 2021[83]

	EU/EEA, reported on 12 August 2021			
	Mild	**Hosp**	**Severe**	**Fatal**
Total N	1,948,252	356,472	52,365	109,878
Asplenia (%)	0	0	0	0
Asthma (%)	0.6	1.2	1.3	1.2
Cancer, malignancy (%)	3.1	9.1	10	11.1
Cardiac disorder, excluding hypertension (%)	9.1	23.7	22.8	29.4
Chronic lung disease, excluding asthma (%)	1.8	3.6	4.4	3.6
Current smoking (%)	0.9	0.1	0.2	0
Diabetes (%)	5	17.1	20.5	19.2
Haematological disorders (%)	0	0.2	0.1	0.1
HIV/other immune deficiency (%)	0.2	0.7	0.7	0.5
Hypertension (%)	0.8	2.9	3.2	3.8
Kidney-related condition, renal disease (%)	0.3	1.8	1.9	2.7
Liver-related condition, liver disease (%)	0.3	0.7	0.7	0.6
Neuromuscular disorder, chronic neurological (%)	0.7	1.8	1.4	2.4
Obesity (%)	0.1	0.2	0.5	0.2
Other endocrine disorder, excluding diabetes (%)	0.3	0.2	0.1	0.1
Rheumatic diseases including arthritis (%)	0	0	0	0
Tuberculosis (%)	0	0	0	0
None (%)	76.7	36.7	32.3	25

Abbreviation: Hosp = Hospitalised

Table 10 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.[31] 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 10. 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[31]

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

In a retrospective cohort of 135,794 individuals under the age of 25 who were tested for COVID-19 by 08 September 2020 within the PEDSnet network of US paediatric health systems, the proportion of obese individuals was similar among those who tested negative (18%) and among mild or asymptomatic COVID-19 cases (19%), but clearly elevated among severe COVID-19 cases (37%)[84]. Those with severe cases of COVID-19 more commonly had chronic conditions in at least two body systems, with 25% of COVID-19 negative individuals, 17% mild or asymptomatic cases, and 38% of severe cases having multiple chronic conditions. More recent data provide insight into comorbidities among the paediatric population. For the period January 01- March 31, 2021 across 14 states, the CDC's COVID-NET database recorded 204 adolescents aged 12-17 who were hospitalized for likely primarily COVID-related reasons.[85] Among the 204 adolescents, 70.6% had at least one major underlying medical condition, the most common conditions being obesity (35.8%), chronic lung diseases including asthma (30.9%), and neurologic disorders (14.2%).[85]

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.[86] 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.[87] 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 faeces 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 radiolabelled 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, faeces, 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.[88]

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[89] 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.[90] 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 (foetuses 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 11. There was no evidence of vaccine-elicited disease enhancement.

Table 11. 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[89], 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 transient decreases are anticipated to be slight and are not likely to be clinically meaningful.
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. [88] 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 12, Table 14, Table 20, Table 22, Table 24, and Table 26) 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% (1/10000) and a probability of 95% of detecting an AE with a frequency of 0.02% (1/5000).

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, MAH 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 on 13 March 2021.

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

For evaluation of booster effects and/or protection against emerging SARS-CoV-2 variants of concern, approximately 600 existing Phase 3 participants 18 to 55 years of age were randomized 1:1 to receive a booster (Dose 3) at 30 µg of either BNT162b2 or a prototype based upon the B.1.351 (Beta) variant that originated in South Africa, BNT162b2SA, approximately 6 months after their second dose of BNT162b2.

The results for Study C4591001 Phase 3 participants 18 to 55 years of age who received the BNT162b2 booster are provided below.

Further evaluation for the paediatric population (5-<12 years of age) has been conducted in study C4591007.

Phase 1 is the dose finding portion of the study. Dose levels were tested in sentinel cohorts of children by age de-escalation, starting with the lowest dose level in the oldest age group. For each age group, the dose level identified as safe and tolerable and immunogenic in C4591007. Phase 1 was advanced for further evaluation in Phase 2/3.

Phase 2/3 (which is ongoing) was planned to evaluate BNT162b2 at the selected dose levels for each age group for safety and tolerability, immunogenicity, and efficacy (depending on meeting success criteria for immunobridging and accrual of a sufficient number of COVID-19 cases). An immunobridging analysis was designed to compare SARS-CoV-2 neutralizing antibody responses in paediatric participants within each age group in Study C4591007 to a group of young adult participants 16 to 25 years of age in the C4591001 efficacy study.

Ongoing[2] Pfizer-BioNTech COVID-19 mRNA vaccine interventional clinical studies also include:

- C4591005: *A phase 1/2 study placebo-controlled, randomized, and observer-blind study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 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[3]: *A phase 2/3 placebo-controlled, randomized, observer-blind 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.* A total of 348 (209 in phase 2 and 139 in phase 3) pregnant women at 24 to 34 weeks gestation were randomised in a 1:1 ratio to vaccine or placebo.

- C4591020 *A phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of multiple formulations of the vaccine candidate BNT-162B2 against Covid-19 in healthy adults 18 through 55 years of age.*

- C4591031 *A phase 3 master protocol to evaluate additional dose(s) of BNT162B2 in healthy individuals previously vaccinated with BNT162B2*.

- 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 and immunocompromised adults.*

- BNT162 03[4] *Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b1) in Chinese healthy subjects: A phase I, randomized, placebo- controlled, observer-blind study*.

- BNT162-04 *A multi-site, phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of a prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 using different dosing regimens in healthy adults*.

- BNT162-06[4] *Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b2) in Chinese healthy population: A phase II, randomized, placebo-controlled, observer-blind study.*

[2] Study C4591017 was completed and therefore is removed from this list

[3] Enrolment of participants into study C4591015 was stopped on 25 October 2021 due to recruitment challenges as a result of global recommendations for COVID-19 vaccination in pregnant women and the increased availability of COVID-19 vaccines. Participants already enrolled will continue follow up evaluations until study end as planned.

[4] This study is conducted by Shanghai Fosun Pharmaceutical Development, Inc. and sponsored by BioNTech SE.

- BNT162-14 *A Phase II, open-label, rollover trial to evaluate the safety and immunogenicity of one or two boosting doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects.*

- BNT162-17 *A Phase II trial to evaluate the safety and immunogenicity of a SARS-CoV-2 multivalent RNA vaccine in healthy subjects.*

- B7471026 *A phase 3, randomized, double blind trial to describe the safety and immunogenicity of 20 valent pneumococcal conjugate vaccine when coadministered with a booster dose of BNT162b2 in adults 65 years of age and older.*

Population for analysis of CT data in this RMP includes the following 3 trials:

- C4591007; Phase 1/2/3, Phase 1 - open label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3- placebo-controlled, observer- blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children and young adults.

- C4591001: Phase 1/2/3, placebo-controlled, randomised, observer-blind, dose-finding, study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals.

- BNT162-01: A multi-site, phase I/II, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy adults.

Participants 16 years of age and older

At the cut-off date of 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 12 through Table 31.

In addition, exposure in clinical studies in special populations is provided in Table 32, Table 33, Table 34, Table 35.

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 12, Table 14, Table 20, Table 24, and Table 26.

Booster dose participants 18 years and older

Study C4591001

At the cut-off date of 17 June 2021, a total of 306 participants, 18 to 55 years of age (of the approximately 600 originally randomized), received BNT162b2 30 µg as booster dose (Dose 3); these participants were originally randomized in the Phase 3 study and completed the BNT162b2 (30 µg) two-dose series, and then received a third dose of BNT162b2 (30 µg) approximately 6 months after receipt of Dose 2, with safety and immune response evaluations at 1 month after Dose 3.

Exposure to BNT162b2 for participants who received the booster dose, by number of doses and demographic characteristics, is shown in Table 36 and Table 37. In addition, exposure in special population who received the booster dose is provided in Table 38.

Participants aged 5 to <12 years of age

As of the cut-off date of 06 September 2021, a total of 48 participants in Phase 1 and of 1518 participants in Phase 2/3 were vaccinated in the Pfizer BioNTech COVID-19 Vaccine clinical development program:

Clinical study exposure data for the 5 to <12 years of age are provided for the ongoing study C4591007 at the cut-off date of 06 September 2021. In this study, 1515 participants received 2 doses and 3 received 1 dose of Pfizer BioNTech COVID-19 Vaccine in the Blinded-Placebo Controlled Follow-up period.

Exposure to Pfizer-BioNTech COVID-19 Vaccine for participants aged 5- to <12 years of age by number of doses and demographic characteristics for Phase 1 are shown in Table 39, Table 40, Table 41 and Table 42; for Phase 2/3 are shown in Table 43, Table 44, Table 45 and Table 46.

Exposure in participants 12 years of age and older (Study C4591001)

Table 12. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Blinded Placebo-Controlled Follow-up Period

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

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

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥16 years to ≤17 years		
Vaccine 30 µg		
1 Dose	3	3
≥18 years to ≤55 years		
Vaccine 30 µg		
1 Dose	58	58
>55 years to ≤64 years		
Vaccine 30 µg		
1 Dose	17	17
≥65 years to ≤74 years		
Vaccine 30 µg		
1 Dose	8	8
≥75 years to ≤84 years		
Vaccine 30 µg		
1 Dose	1	1
≥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 14. Exposure to BNT162b2 by Age Group and Dose (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

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

Table 14. 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

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 15. 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		

Table 15. 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
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 15. 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

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Table 16. 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 17. 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 18. 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 19. 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 20. 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 21. 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 22. 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 23. 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 24. 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 24. 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 24. 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 24. 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 24. 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 25. 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 25. 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 25. 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 26. 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 26. 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 26. 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 26. 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 27. 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 27. 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 27. 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 28. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 10 µg		
Racial origin		
White	23	46
Asian	1	2
Total	24	48
Ethnic origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	23	46
Total	24	48
Vaccine 20 µg		
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 29. 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 30. 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 31. 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 32. 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 33. 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 34. Exposure to BNT162b2 (30 µg) by Special Population (C4591001) – Blinded Placebo-Controlled Follow-up Period

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

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

Table 35. Exposure to BNT162b2 (30 µg) by Special Population (C4591001) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding

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

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

Booster dose participants 18 years and older

Table 36. Exposure to BNT162b2 by Dose, Age Group, and Gender (C4591001) – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) –Booster Safety Population

	Number of Subjects Exposed to BNT162b2	
Dose Age Group[a]	Male	Female
Vaccine 30 µg		
≥18 years to ≤55 years	140	166
Total	140	166

Note: Only phase 3 subjects who already received two doses of BNT162b2 in the original phase of the study and consented to participate the booster evaluation phase were rerandomized to receive booster dose.
a. Based on age at booster dose.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (23:01) Source Data: adsl Table Generation: 17AUG2021 (09:15)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1_PVP/adsl_boost_s932

Table 37. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001) –BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) –Booster Safety Population

Age Group[a] Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2
Subjects ≥18 years to ≤55 years	
Vaccine 30 µg	
Racial origin	
White	249
Black or African American	28
Asian	16
American Indian or Alaska Native	2
Native Hawaiian or other Pacific Islander	1
Multiracial	4
Not reported	6
Total	306
Ethnic origin	
Hispanic/Latino	85
Non-Hispanic/non-Latino	219
Not reported	2
Total	306

Note: Only phase 3 subjects who already received two doses of BNT162b2 in the original phase of the study and consented to participate the booster evaluation phase were rerandomized to receive booster dose.
a. Based on age at booster dose.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (23:01) Source Data: adsl Table Generation: 17AUG2021 (09:16)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1_PVP/adsl_boost_s942

Table 38. Exposure to BNT162b2 (30 µg) by Special Population (C4591001) – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) –Booster Safety Population

Population	Number of Subjects Exposed to BNT162b2 (30 µg) (Na=306)[nb]
Subjects with any baseline comorbidity	155
Any Malignancy + Metastatic Solid Tumor + Leukemia + Lymphoma	8
Chronic Pulmonary Disease	40
Mild Liver Disease + Moderate or Severe Liver Disease	5
Cerebrovascular Disease + Peripheral Vascular Disease + Myocardial Infarction + Congestive Heart Failure	1
Diabetes With/Without Chronic Complication	6
Obese	122

Note: Comorbidity is based Charlson Comorbidity Index categories. Participants identified as belonging to these categories were identified by medical history data collected during the study.
Note: Only phase 3 subjects who already received two doses of BNT162b2 in the original phase of the study and consented to participate the booster evaluation phase were rerandomized to receive booster dose.
Note: Hemiplegia or Paraplegia only includes preferred terms Hemiplegia and Paraplegia.
a. N = number of subjects in the specified group.
b. n = Number of subjects reporting at least 1 occurrence of any comorbidity or obese (BMI ≥30 kg/m2 [≥16 Years of age].
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (13:46) Source Data: admh Table Generation: 17AUG2021 (09:16)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1_PVP/admh_boost_s953

Exposure in participants 5 to <12 years of age (Study C4591007) - Phase 1

Table 39. Exposure to BNT162b2 by Age Group and Dose (C4591007) – Phase 1 – Open Label

Age Group Dose Exposure (Number of Doses Received)	Number of Participants Exposed to BNT162b2	Total Number of Vaccine Doses
5 years to <12 years		
Vaccine 10 µg		
1 Dose	12	12
2 Doses	16	32
Total	28	44
Vaccine 20 µg		
2 Doses	16	32
Total	16	32
Vaccine 30 µg		
1 Dose	12	12
2 Doses	4	8
Total	16	20

Note: Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2 and 12 participants received 10 µg at Dose 2.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adsl Table Generation: 13SEP2021 (22:16) (Cutoff date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: (CDISC)/C4591007_P1_RMP_PVP/adsl_s911

Table 40. Exposure to BNT162b2 by Age Group, Dose, and Gender (C4591007) – Phase 1 – Open Label

	Number of Participants Exposed to BNT162b2		Total Number of Vaccine Doses	
Age Group Dose	Male	Female	Male	Female
5 years to <12 years				
Vaccine 10 µg	11	17	16	28
Vaccine 20 µg	10	6	20	12
Vaccine 30 µg	9	7	12	8
Total	24	24	48	48

Note: Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2 and 12 participants received 10 µg at Dose 2.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adsl Table Generation: 13SEP2021 (22:18) (Cutoff date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: (CDISC)/C4591007_P1_RMP_PVP/adsl_s931

Table 41. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 1 – Open Label

Age Group Dose Race/Ethnic Origin	Number of Participants Exposed to BNT162b2	Total Number of Vaccine Doses
Participants 5 years to <12 years		
Vaccine 10 µg		
Racial origin		
White	21	32
Black or African American	3	6
Asian	3	5
Multiracial	1	1
Total	28	44
Ethnic origin		
Hispanic/Latino	2	4
Non-Hispanic/non-Latino	26	40
Total	28	44
Vaccine 20 µg		
Racial origin		
White	13	26
Asian	2	4
American Indian or Alaska Native	1	2
Total	16	32
Ethnic origin		
Non-Hispanic/non-Latino	16	32
Total	16	32
Vaccine 30 µg		
Racial origin		
White	14	18
Asian	1	1
Multiracial	1	1
Total	16	20
Ethnic origin		
Hispanic/Latino	2	4
Non-Hispanic/non-Latino	14	16
Total	16	20

Note: Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2 and 12 participants received 10 µg at Dose 2.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adsl Table Generation: 13SEP2021 (22:20) (Cutoff date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: (CDISC)/C4591007_P1_RMP_PVP/adsl_s941

Table 42. Exposure to BNT162b2 by Special Population (C4591007) – Phase 1 – 5 to <12 Years of Age – Open Label

Population	Number of Participants Exposed to BNT162b2 (10 µg) (Nc=16) nd	Number of Participants Exposed to BNT162b2 (20 µg) (Nc=16) nd	Number of Participants Exposed to BNT162b2 (30/30[a] µg) (Nc=4) nd	Number of Participants Exposed to BNT162b2 (30/10b µg) (Nc=12) nd	Total Number of Vaccine Doses
Participants with any baseline comorbidity[e]	1	2	0	1	8
Asthma	1	0	0	1	4
Obese[f]	0	2	0	0	4

a. Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2.
b. Of the 16 participants who received 30 µg at Dose 1, 12 participants received 10 µg at Dose 2.
c. N = number of participants in the specified group.
d. n = Number of participants reporting at least 1 occurrence of any comorbidity or obese (BMI ≥ 95th percentile).
e. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥ 95th percentile).
f. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: admh Table Generation: 15SEP2021 (13:22) (Cutoff date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: (CDISC)/C4591007_P1_RMP_PVP/admh_s953_p1

Exposure in participants 5 to <12 years of age (Study C4591007) – Phase 2/3

Table 43. Exposure to BNT162b2 by Age Group and Dose (C4591007) – Phase 2/3 – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Exposure (Number of Doses Received)	Number of Participants Exposed to BNT162b2	Total Number of Vaccine Doses
5 years to <12 years		
Vaccine 10 µg		
1 Dose	3	3
2 Doses	1515	3030
Total	1518	3033

PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (23:25) Source Data: adsl Table Generation: 15SEP2021 (11:51) (Cutoff date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: (CDISC)/C4591007_RMP_PVP/adsl_s912

Table 44. Exposure to BNT162b2 by Age Group, Dose, and Gender (C4591007) – Phase 2/3 – Blinded Placebo-Controlled Follow-up Period

	Number of Participants Exposed to BNT162b2		Total Number of Vaccine Doses	
Age Group Dose	Male	Female	Male	Female
5 years to <12 years				
Vaccine 10 µg	799	719	1596	1437
Total	799	719	1596	1437

PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (23:25) Source Data: adsl Table Generation: 15SEP2021 (11:51) (Cutoff date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: (CDISC)/C4591007_RMP_PVP/adsl_s932

Table 45. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 2/3 – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Race/Ethnic Origin	Number of Participants Exposed to BNT162b2	Total Number of Vaccine Doses
Participants 5 years to <12 years		
Vaccine 10 µg		
Racial origin		
White	1204	2405
Black or African American	89	178
Asian	90	180
American Indian or Alaska Native	12	24
Native Hawaiian or other Pacific Islander	5	10
Multiracial	109	218
Not reported	9	18
Total	1518	3033
Ethnic origin		
Hispanic/Latino	319	638
Non-Hispanic/non-Latino	1196	2389
Not reported	3	6
Total	1518	3033

PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (23:25) Source Data: adsl Table Generation: 15SEP2021 (11:51) (Cutoff date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: (CDISC)/C4591007_RMP_PVP/adsl_s942

Table 46. Exposure to BNT162b2 by Special Population (C4591007) – Phase 2/3 – 5 to <12 Years of Age – Blinded Placebo-Controlled Follow-up Period

Population	Number of Participants Exposed to BNT162b2 (10 µg) (Na=1518) nb	Total Number of Vaccine Doses
Participants with any baseline comorbidityc	312	623
Asthma	119	237
Blood disorders	1	2
Cardiovascular disease	8	16
Chronic lung disease	1	2
Chronic metabolic disease	2	4
Congenital heart disease	15	30
Diabetes mellitus	2	4
Feeding tube dependent	2	4
Immunocompromised condition	1	2
Neurologic disorder	19	38
Obesed	174	348
Sickle cell disease	1	2

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; MMWR = Morbidity and Mortality Weekly Report.
a. N = number of participants in the specified group.
b. n = Number of participants with the specified characteristic. Participants with multiple occurrences within each category are counted only once.
c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥ 95th percentile).
d. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (17:20) Source Data: admh Table Generation: 15SEP2021 (11:51) (Cutoff date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: (CDISC)/C4591007_RMP_PVP/admh_s953_p2

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: Maternal vaccination with COVID 19 mRNA vaccine is being studied in C4591015 to explore 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 47. 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 5 to <12 years of age** Through the cut-off date of 06 September 2021, there were no CT cases of pregnancy from study C4591007. **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 cut-off date of 13 March 2021, there were 50 cases (52 events) originating from Study C4591001, and all were unique pregnancies.

Table 47. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
	Participants in Booster dose group Through the cut-off date of 17 June 2021, there were no cases indicative of exposure during pregnancy originating from Study C4591001 in participants enrolled in the booster group.
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 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, complicated by underlying risks, is susceptible to disease prevented by the vaccine. **Participants 5 to <12 years of age** Through the cut-off date of 06 September 2021, there were no cases indicative of exposure during breastfeeding from study C4591007. **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 cut-off date of 13 March 2021, there were no CT cases indicative of exposure during breastfeeding. **Participants in Booster dose group** Through the cut-off date of 17 June 2021, there were no cases indicative of exposure during breastfeeding originating from Study C4591001 in participants enrolled in the booster group.
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 5 to < 12 years of age** Please refer to Table 42 and Table 46 for the exposure of special populations. **Participants 12 to 15 years of age** Please refer to Table 32 and Table 33 for the exposure of special populations.

Table 47. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
	Participants 16 years of age and older Please refer to Table 34 and Table 35 for the exposure of special populations. **Participants in Booster dose group** Please refer to Table 38 for the exposure of special populations.
Population with relevant different ethnic origin/race	Please refer to Table 24 to Table 31 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 aged less than 5 years of age have not yet been established. Limited data are available. **Participants 5 to < 12 years of age** A total of 48 participants in Phase 1, 5 to < 12 years of age and of 1518 participants in Phase 2/3 received Pfizer BioNTech COVID-19 Vaccine through the cut-off date of 06 September 2021. **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 12 and Table 14). **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 12 and Table 14).
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 12) • 4237 participants in the open-label follow-up period after unblinding (Table 14) 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 15). **Participants in Booster dose group** Through the cut-off date of 17 June 2021, there were no elderly participants (≥65 years old) from Study C4591001 enrolled in the booster group.

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, considering that approximately 82% of the shipped doses were administered; this estimation is a weight average considering the proportion of doses administered out of those shipped upon review of data currently available for the EU-EEA[5] countries and the US[6].

With these caveats in mind, it is estimated that:

- approximately 1,709,812,866 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 30 September 2021, corresponding to approximately 1,402,241,841 estimated administered doses.

- The estimated cumulative number of shipped and administered doses of BNT162b2 by region7 based on data provided in the shipment tracker (Order Book)8 from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 30 September 2021, are summarised in Table 48.

[5] Approximately 81% 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 01 October 2021.

[6] Approximately 84% 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 02 October 2021.

[7] Currently there are no available data that allow to estimate exposure by gender; for age group data available for some EU-EEA countries see below data in Table 50.

[8] 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 Fosun License Partner territories, Hong Kong and Macau, were provided by BioNTech.

Table 48. Cumulative Estimated Shipped/Administered Doses of BNT162b2 by Region Worldwide

Region/Country/Other	% of Doses	Total Number of Shipped Doses	Total Number of Administered Doses
Europe	**41.1%**	**703267110**	**571473911**
European Union[a] (27)	30.0%	513505785	415939686
Additional EEA[a] Countries (3)	0.4%	7006155	5674986
Switzerland[a]	0.3%	4500990	3690812
UK[b]	3.6%	61213230	50194849
Other Countries[c]	6.3%	107217045	87917977
Commonwealth of Independent States[d]	0.6%	9823905	8055602
North America[e]	**18.5%**	**316093695**	**264597240**
US	15.8%	270020505	226817224
Canada	2.7%	46073190	37780016
Central and South America[f]	12.5%	213085680	174730258
Asia	23.6%	404077581	331343616
Japan[a]	10.7%	183498120	150468458
Other Countries[g]	12.9%	220579461	180875158
Oceania	1.4%	23158980	18990364
Australia/New Zealand[a]	1.4%	23158980	18990364
Other Countries	0.0%	0	0
Africa[h]	2.9%	50129820	41106452
Total	100.0%	1709812866	1402241841

Table 48. Cumulative Estimated Shipped/Administered Doses of BNT162b2 by Region Worldwide

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

a. In this Region BNT162b2 was conditionally approved;
b. In the UK, both the authorisation for emergency supply under regulation 174 and the conditional marketing authorisation approval are currently active for BNT162b2;
c. Includes Albania, Kosovo and North Macedonia where BNT162b2 was conditionally approved, Serbia where it received authorization for emergency supply, Bosnia where it was shipped for COVAX, Turkey where it was shipped according to a pharmacovigilance agreement in place by the MAH and the Turkish government.
d. Includes Georgia and Ukraine where BNT162b2 received authorization for emergency supply and Moldova where it was conditionally approved; in Azerbaijan BNT162b2 was shipped for COVAX, and Tajikistan and Uzbekistan are part of US government donations.
e. In this Region BNT162b2 initially received authorization for emergency supply; in the US, a full approval (BLA) was also granted on 23 August 2021 and in Canada a full approval (NDS) replacing the pre-existing authorization for emergency supply was granted during the current reporting period on 16 September 2021.
f. Includes Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Honduras, Mexico, Panama, Paraguay and Uruguay where BNT162b2 received authorisation for emergency supply, Argentina, Brazil and Peru where BNT162b2 was conditionally approved; Bolivia and Guatemala where BNT162b2 was shipped for COVAX and Antigua&Barbuda, Bahamas, Barbados, Belize, Dominica, Grenada, Guyana, Jamaica, St Kitts&Nevis, St. Lucia, StVin&Grenadine, Suriname and Trinidad&Tobago that are part of US Government donations;
g. Includes Bahrain, Bhutan, Indonesia, Iraq, Israel, Jordan, Kuwait, Lebanon, Macau, Maldives, Mongolia, Oman, Pakistan, Palestine, Philippines, Qatar, Saudi Arabia, Singapore, Sri Lanka, United Arab Emirates and Vietnam where BNT162b2 received authorization for emergency supply; Hong Kong, Malaysia, South Korea and Thailand where BNT162b2 was conditionally approved and Bangladesh, Laos and West Bank & Gaza where BNT162b2 was shipped for COVAX;
h. Includes Angola, Cape Verde, Chad, Ivory Coast, Lybia and Togo where BNT162b2 was shipped for COVAX; Benin, Congo, Gabon, Namibia, Seychelles, Sierra Leone and Uganda that are parts of US Government donations; Botswana, Egypt, Eswatini, Kenya, Mauritius, Morocco, Rwanda, South Africa and Tunisia where BNT162b2 received authorisation for emergency supply.

Cumulative Exposure Data in the EU-EEA

Estimated shipped doses in the EU-EEA countries may serve as a reasonable indicator of subject exposure in these countries, considering that approximately 81% of the shipped doses were administered; this estimation is based on the proportion of doses administered out of those shipped upon review of data currently available for the EU countries.

With these caveats in mind, it is estimated that approximately 520,511,940 doses of BNT162b2 were shipped in the EU-EEA countries from the receipt of the first conditional marketing authorisation approval on 21 December 2020 through 30 September 2021, corresponding to 421,614,671 estimated administered doses.

Table 49 provides the estimated cumulative number of shipped doses of BNT162b2 from the receipt of the first conditional marketing authorisation approval through 30 September 2021 for the 27 EU Countries and for the 3 EEA Countries.

Table 49. Cumulative Estimated Shipped/Administered Doses of BNT162b2 by EU-EEA Countries (30)

EU Country	Total Number of Cumulative Shipped Doses	Total Number of Cumulative Administered Doses
EU (27)	**513505785**	**415939686**
Austria	10160865	8230301
Belgium	13933335	11286001
Bulgaria	4233450	3429095
Croatia	2955420	2393890
Cyprus	1047540	848507
Czech Republic	11667240	9450464
Denmark	8148660	6600415
Estonia	1101945	892575
Finland	6740955	5460174
France	82660500	66955005
Germany	99147945	80309835
Greece	12178920	9864925
Hungary	9292725	7527107
Ireland	6499350	5264474
Italy	71408610	57840974
Latvia	1382745	1120023
Lithuania	3232125	2618021
Luxembourg	715455	579519
Malta	803985	651228
Netherlands	20845110	16884539
Poland	45795360	37094242
Portugal	11977290	9701605
Romania	12710880	10295813
Slovakia	4743180	3841976
Slovenia	2068755	1675692
Spain	55768830	45172752
Sweden	12284610	9950534
EEA (3)	**7006155**	**5674986**
Iceland	430365	348596
Liechtenstein	0	0
Norway	6575790	5326390
Total	**520511940**	**421614671**

Table 50 provides cumulatively the estimated number of persons who received 1 dose or 2 doses of BNT162b2, in total, and by age group where available, in the EU EEA countries.

Table 50. Cumulative Administered 1&2 doses of BNT162b2 by Age Group in EU EEA Countries[a]

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	204007	167957	29846	26719	135443	125025	726731	686745	624862	599225	412920	397085	418347	402626	3835758	3603152
Belgium	589926	529402	57495	54822	220551	214529	894786	886421	861116	856307	546371	542545	384275	377571	5467018	5356364
Bulgaria	8805	6756	29827	26060	249990	228514	146883	136812	174292	163781	134345	126330	42294	39505	778258	721456
Croatia	10198	7386	72797	63278	429224	391107	247700	231999	262924	250867	155171	149146	69166	65904	1236982	1152301
Cyprus			40818	37676	181014	171481	59143	57160	46048	44777	26099	25545	26870	26292	379992	362931
Czechia	238927	213725	32069	30475	191650	186753	813394	802280	788464	779309	575912	569499	255283	250682	4670256	4574061
Denmark	0	0	36773	36349	106123	107833	665491	687024	566075	577443	523584	524529	238662	239178	3422782	3470003
Estonia	33830	27335	37985	30954	188214	163835	74692	67991	64055	59013	60702	58044	43151	41679	468799	421516
Finland	174058	33035	26303	13193	117702	939448	521733	514571	375193	414376	460319	448011	258908	249995	3056216	2698335
France															38823243	33797918
Germany															39125277	40854874
Greece	148858	77063	30324	23992	151151	136769	872423	836208	563811	544557	641728	629998	528392	517721	4421112	4136110
Hungary	286873	230551	17132	15587	965075	911026	341002	328090	394087	381986	319553	312875	210967	205514	2402013	2295368
Iceland			14257	14207	57012	56884	17487	18610	14729	15532	8589	8676	13516	13446	125590	127355
Ireland	272252	206843	24198	22414	116325	112764	372455	369446	97291	96206	311562	309664	173641	170510	2360192	2297618
Italy	1902877	1342475	2550420	2174777	10520968	9318610	5794957	5404835	3582760	3345821	2660192	2513966	3649561	3489690	28758858	26247699
Latvia	40184	34086	48379	42681	217191	196880	81518	73233	63075	56734	28149	25009	12001	10480	450311	405016
Liechtenstein															7246	5846
Lithuania	57199	48627	95921	85154	399741	361733	200696	185441	191023	181762	116173	111870	65767	63443	1069321	989403
Luxembourg			19734	18079	111779	109594	53247	52224	35804	35268	13618	13359	20021	19605	254203	248129
Malta	19500	18766	19689	19381	103590	102385	23669	22276	20243	18552	39848	39581	22347	22152	229616	224325

Table 50. Cumulative Administered 1&2 doses of BNT162b2 by Age Group in EU EEA Countries[a]

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
Netherlands															8741090	7924048
Norway	186620	13145	333697	201436	1206580	824954	548728	494121	483709	478742	413080	405706	214040	208107	3199834	2613066
Poland			841459	804100	4594857	4447527	1966733	1930026	2070471	2038356	2185007	2163046	1093218	1076257	12751745	12459312
Portugal	538207	408197	337012	284818	2008157	1833753	940743	893145	639894	615705	497870	482958	589250	570486	5012926	4680865
Romania	91824	81689	272820	258747	1425327	1387325	688289	674640	787359	774228	464478	456217	154174	150036	3825480	3717677
Slovakia			126820	118069	605294	579316	211589	204787	278104	272722	245538	242086	88538	85919	1555883	1502899
Slovenia	28504	19454	38874	30468	194650	152572	128549	108384	133008	118176	114905	105847	76014	70266	686000	585713
Spain	2058854	1541928	1802100	1403357	9701548	8512941	4682215	4318927	1191832	1123085	3552166	3526874	2696180	2661157	23626041	21546341
Sweden			426065	345936	2112307	1936318	966831	958163	728378	723465	568343	558142	427029	411292	5228953	4933328
Grand Total	6891503	5008420	9650122	8194736	4566002	4146285	2204164	2094359	1503860	1456595	1507622	1474608	1177162	1143953	20597095	19395329

a. Source is https://covid19-vaccine-report.ecdc.europa.eu/ (point 6). Please consider that data for cumulative period are available on this website only as of week 37, 19 September 2021.

b. Population may include also subjects of unknown age.

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 51.

Table 51. 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, Dose 2, and Dose 3. 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.

Participants 5 to <12 years of age

Phase 1 and Phase 2/3 participants or their parent/legal guardian were to monitor and record reactogenicity for 7 days after each dose; in the 5 to <12 years of age group, events included:

- **Local reactions:** pain, redness, swelling at the injection site

Overall, the pattern of local reactions reported in children 5 to <12 years of age after each dose was generally similar to that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001 with regard to pain at the injection site, but children had slightly higher frequencies of swelling and redness at the injection site (still within tolerable limits).

- **Systemic events:** fever, fatigue, headache, chills, vomiting, diarrhoea, new or worsened muscle pain, new or worsened joint pain

Overall, the pattern of systemic events reported in children 5 to <12 years of age after each dose was generally comparable to, or less than, that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001.

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)[91]

- ACCESS protocol[92]
- US CDC (preliminary list of AESI for VAERS surveillance)[93]
- 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 (eg. 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 neither in clinical studies nor in the post-authorization experience 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 fully known in pregnant or breastfeeding women due to their initial exclusion from the pivotal clinical study however, post-marketing experience in pregnant women is available.[94] Additionally one clinical study of the safety and immunogenicity of the COVID-19 vaccine in pregnant women is ongoing (C4591015); 2 non-interventional studies (C4591009 and C4591011) to assess whether sub-cohorts of interest, such as pregnant women, experience increased risk of safety events of interest following receipt of the COVID-19 vaccine are planned and another 2 non-interventional studies, C4591021 and C4591022, are ongoing.

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. A non-interventional study [C4591024 (former Safety and immunogenicity in high-risk adults)] to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age is approved.

Missing Information: Use in frail patients with co-morbidities (eg. 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. One protocol study (C4591030 - *Co-administration study with seasonal influenza vaccine*) is planned.

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 and 2 non-interventional studies (C4591036 and C4591038) are planned.

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 52. Anaphylaxis [a]

Potential mechanisms, evidence source and strength of evidence	Interaction of an allergen with IgE on basophils and mast cells triggers release of histamine, leukotrienes and other mediators that cause diffuse smooth muscle contraction and vasodilation with plasma leakage. This can manifest clinically with dyspnoea, hypotension, swelling (sometimes leading to airway compromise), and rash (including hives).
Characterisation of the risk	***Participants 5 to <12 years of age*** **Data from the CT dataset (study C4591007)** Anaphylactic reaction/shock, Anaphylactoid reaction/shock were not observed through the cut-off date of 06 September 2021. **Data from the safety database (non-CT)** Through 18 June 2021, there were no cases reporting Anaphylactic reaction/shock, Anaphylactoid reaction/shock involving individuals 5 to <12 years of age. ***Participants 12 to 15 years of age*** **Data from the CT database[b]** Through 30 September 2021 there were no cases reporting Anaphylactic reaction/shock, Anaphylactoid reaction/shock as SAEs from the CT dataset. **Data from the safety database (non-CT)** Through 30 September 2021, there were 43 cases in individuals 12 to 15 years of age, reporting 46 relevant events of Anaphylactic reaction (41), Anaphylactic shock (4) and Anaphylactoid reaction (1); overall event seriousness and outcome are summarized below.

	Total Events N = 46
Serious events	46
Events with Criterion of Hospitalization	15
Distribution of events by Outcome	
Outcome: Death	0
Outcome: Resolved/Resolving	32
Outcome: Not resolved	2
Outcome: Unknown	12

Booster Dose (Participants 12 to 15 years of age)

Data from the safety database (non-CT)

Through 30 September 2021, no cases were retrieved reporting anaphylaxis.

Participants 16 years of age and older

Data from the CT database[b]

Through 30 September 2021, there were 2 cases from the CT dataset, from Phase 3 clinical study C4591001: 1 case of serious Anaphylactoid reaction reported as resolved and deemed related to study treatment by the Investigator, and 1 case of

Table 52. Anaphylaxis [a]

<table>
<tr><td>Characterisation of the risk
(Cont'd)</td><td>serious Anaphylactic reaction reported as resolved and deemed not related to study treatment by the Investigator.

<u>Data from the safety database (non-CT)</u>
Through 30 September 2021 there were 6327 cases (1.0% of the total post authorization dataset) reporting a total of 6524 events in individuals 16 years and older including:
Anaphylactic reaction (5581), Anaphylactic shock (800), Anaphylactoid rection (135) and Anaphylactoid shock (8).

Overall event seriousness and outcome are summarized below.

<table>
<tr><th></th><th>Total Events
N = 6524 (%)</th></tr>
<tr><td>Serious events</td><td>6521 (100)</td></tr>
<tr><td>Events with Criterion of Hospitalization</td><td>2128 (32.6)</td></tr>
<tr><td colspan="2">Distribution of events by Outcome</td></tr>
<tr><td>Outcome: Death</td><td>39 (0.6)</td></tr>
<tr><td>Outcome: Resolved/Resolving</td><td>4881 (74.8)</td></tr>
<tr><td>Outcome: Not resolved</td><td>339 (5.2)</td></tr>
<tr><td>Outcome: Resolved with sequelae</td><td>97 (1.5)</td></tr>
<tr><td>Outcome: Unknown</td><td>1174 (18)</td></tr>
</table>

Booster Dose (Participants 16 years of age and older)

<u>Data from the CT database (Study C4591001)</u>
Through 17 June 2021, no cases were retrieved reporting anaphylaxis in the participants who received booster dose.
<u>Data from the safety database (non-CT)</u>
Through 30 September 2021, there were 4 cases among subjects who received a booster: 2 subjects experienced Anaphylactic reaction with outcome resolved and another 2 experienced Anaphylactic shock with outcome unknown. Three (3) subjects received the initial 2-dose regimen of BioNTech COVID-19 Vaccine, 1 previously received 2 doses of an unknown COVID-19 vaccine. One of these 4 subjects was immunocompromised.
<u>Conclusion</u>: Evaluation of cases of Anaphylactic reaction/shock, Anaphylactoid reaction/shock through 30 September 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.</td></tr>
<tr><td>Risk factors and risk groups</td><td>Known hypersensitivity to any components of the vaccine. As IgE hypersensitivity is known to occur at re-challenge with the allergen in sensitized individuals, the risk of anaphylactic reactions following a 3rd exposure to the same substance is anticipated to be lower in individuals without history of hypersensitivity response to first or second exposure.[95]</td></tr>
<tr><td>Preventability</td><td>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.</td></tr>
<tr><td>Impact on the risk-benefit balance of the biologic product</td><td>Anaphylactic reaction in an individual can be impactful (medically important) because it is a potentially life-threatening event requiring medical intervention.</td></tr>
</table>

Table 52. Anaphylaxis [a]

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

Table 53. Myocarditis and Pericarditis[a]

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 5 to <12 years of age*** **Data from the CT dataset (study C4591007)** Myocarditis and Pericarditis were not observed through the cut-off date of 06 September 2021. **Data from the safety database (non-CT)** Through 18 June 2021, there were no cases reporting myocarditis/pericarditis involving individuals 5 to 11 years of age. ***Participants 12 to 15 years of age*** **Data from the CT dataset[b]:** There were no cases reporting Myocarditis or Pericarditis as SAE in the clinical trial dataset through the cut-off date of 30 September 2021. **Data from the safety dataset(non-CT)** Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 30 September 2021, there were 216 potentially relevant cases of Myocarditis and Pericarditis: 154 cases reported myocarditis and 62 cases reported pericarditis (in 35 of these 216 cases, the subjects developed both myocarditis and pericarditis, unique number was 181 cases). Myocarditis (154 cases) These 154 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:

Table 53. Myocarditis and Pericarditis[a]

Brighton Collaboration Level	Number of cases
BC 1	14
BC 2	9
BC 3	0
BC 4	130
BC 5	1
Total	154

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 Level 3. Overall event seriousness and outcome of the 153 cases meeting BC Levels 1-4 cases are summarized below.

	Total Events N = 153
Serious events	152
Events with Criterion of Hospitalization	110
Distribution of events by Outcome	
Outcome: Death	0
Outcome: Resolved/Resolving	79
Outcome: Not resolved	17
Outcome: Resolved with sequelae	0
Outcome: Unknown/No data	57

Pericarditis (62 cases)

Overall event seriousness and outcome of these 62 cases are summarized below.

	Total Events N = 62
Serious events	62
Events with Criterion of Hospitalization	17
Distribution of events by Outcome	
Outcome: Death	0
Outcome: Resolved/Resolving	18
Outcome: Not resolved	9
Outcome: Resolved with sequelae	1
Outcome: Unknown/No data	34

Booster Dose (Participants 12 to 15 years of age)

Data from the safety database (non-CT)

Through 30 September 2021, no subjects received the booster dose.

Participants 16 years of age and older

Data from the CT dataset[b]

There were 3 cases reporting myocarditis and pericarditis as SAEs in the clinical trial dataset through the cut-off date of 30 September 2021. These cases originated from Phase 3 clinical study C4591001 and are summarized below:

Table 53. Myocarditis and Pericarditis[a]

Myocarditis: 1 case of myocarditis reported as resolved and deemed not related to study treatment by the Investigator.

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

Data from the safety dataset (non-CT)

Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 30 September 2021, there were 5647 potentially relevant cases (0.9% of the total post-authorization dataset): 3165 cases reported myocarditis and 2482 cases reported pericarditis (in 298 of these 5647 cases, the subjects were reported to have developed both myocarditis and pericarditis, unique number was 5349 cases).

Myocarditis (3165 cases):

These 3165 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	312
BC 2	135
BC 3	68
BC 4	2630
BC 5	20
Total	3165

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 3145 cases meeting BC Level 1 to 4, which are presented below:

Reported relevant PTs: Myocarditis (3140), Autoimmune myocarditis (2), Eosinophilic myocarditis, Hypersensitivity myocarditis and Immune-mediated myocarditis (1 each).

Overall event seriousness and outcome of these 3145 cases are summarized below:

	Total Events N = 3145 (%)
Serious events	3129 (99.5)
Events with Criterion of Hospitalization	1999 (63.6)
Distribution of events by Outcome	
Outcome: Death	52 (1.7)
Outcome: Resolved/Resolving	1353 (43)
Outcome: Not resolved	906 (28.8)

Table 53. Myocarditis and Pericarditis[a]

	Outcome: Resolved with sequelae | 73 (2.3) Outcome: Unknown/No data | 763 (24.3) Pericarditis (2482 cases) Reported relevant PTs: Pericarditis (2449), Pleuropericarditis (37) and Pericarditis constrictive (6). Overall event seriousness and outcome of these 2482 cases are summarized below: **Total Events N = 2492 (%)** Serious events | 2484 (99. 7) Events with Criterion of Hospitalization | 1002 (40.2) **Distribution of events by Outcome** Outcome: Death | 10 (0.4) Outcome: Resolved/Resolving | 1256 (50.4) Outcome: Not resolved | 698 (28) Outcome: Resolved with sequelae | 34 (1.4) Outcome: Unknown/No data | 495 (19.9) ***Booster Dose (Participants 16 years of age and older)*** **Data from the CT database (Study C4591001)** Through 17 June 2021, no cases were retrieved reporting myocarditis and pericarditis in the participants who received booster dose. **Data from the safety database (non-CT)** Through 30 September 2021, 6 cases were identified among subjects who received a booster dose: 3 subjects experienced myocarditis (assessed according to BC as level 4) and 3 experienced pericarditis (assessed according to BC as level 4); 3 subjects received a heterologous vaccination cycle, 2 received an initial 2 dose regimen of an unknown COVID-19 vaccine and 1 received the initial 2-dose regimen of the Pfizer-BioNTech vaccine. None was immunocompromised. Overall event seriousness and outcome of these 6 cases are summarized below: **Total Events N = 6** Serious events* | 3 Events with Criterion of Hospitalization | 1 **Distribution of events by Outcome** Outcome: Death | 1 Outcome: Resolved/Resolving | 2 Outcome: Not resolved | 3 Outcome: Resolved with sequelae | 0 Outcome: Unknown/No data | 0 *In 1 case myocarditis was upgraded to serious after the RMP DLP Conclusion: the MAH has updated the labels to include information about myocarditis and pericarditis following vaccine administration; a Direct Healthcare Professional Communication (DHPC) to address these findings was distributed. 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

Table 53. Myocarditis and Pericarditis[a]

	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 favourable 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.
b. 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 54. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) [a]

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.[86,96] 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.[97] 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).[98]
Characterisation of the risk	***Participants 5 to <12 years of age*** **Data from the CT database (study C4591007)** VAED including VAERD were not observed through the cut-off date of 06 September 2021. **Data from the safety database (non-CT)** Through 18 June 2021, there were no cases reporting VAED/VAERD involving individuals 5 to < 12 years of age. ***Participants 12 to 15 years of age*** **Data from the CT database[b]** There were no cases reporting VAED/VAERD as SAEs in the CT dataset through the DLP of 30 September 2021. **Data from the safety database (non-CT)** Through 30 September 2021, there were 2 cases indicative of VAED or VAERD in the safety database involving individuals 12 to 15 years of age. The reported relevant PTs were: Drug ineffective, Diarrhoea, Multisystem inflammatory syndrome in children, Vomiting, and Vaccination failure (1 each); all events were serious requiring hospitalization; 3 of these 5 events resolved and in 2 the outcome was unknown. ***Booster Dose (Participants 12 to 15 years of age)*** **Data from the safety database (non-CT):** Through 30 September 2021, no cases were retrieved reporting a booster dose.

Table 54. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) [a]

Characterisation of the risk *(Cont'd)*

Participants 16 years of age and older

Data from the CT database[b]:

There were no cases indicative of VAED/VAERD as SAEs in the CT dataset through the DLP of 30 September 2021.

Data from the safety database

Through the updated DLP 30 September 2021, there were 1402 cases (0.2% of the total post-authorization dataset), reporting 9233 potentially relevant events.

Seriousness criteria for the total 1402 cases: Medically significant (1126, of which 31 also serious for disability), Hospitalization required (non-fatal/non-life threatening) (474, of which 9 also serious for disability), Life threatening (133, of which 105 were also serious for hospitalization), Death (334).

Gender: Females (707), Males (656), Unknown (39);

Age (n=1340) ranged from 17 to 103 years (mean = 69.6 years, median = 75).

Overall event seriousness and outcome are summarized below.

	Total Events N = 9233 (%)
Serious events	6610 (71.6)
Events with Criterion of Hospitalization	3334 (36.1)
Distribution of events by Outcome[a]	
Outcome: Death	1230 (13.3)
Outcome: Resolved/Resolving	2648 (28.7)
Outcome: Not resolved	1648-(17.8)
Outcome: Resolved with sequelae	68 (0.7)
Outcome: Unknown/No data	3655 (39.6)
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 (844), Vaccination failure (547), Dyspnoea (438), COVID-19 pneumonia (517), Diarrhoea (271).

Booster Dose (Participants 16 years of age and older)

Data from the CT database (Study C4591001)

Through 17 June 2021, no AE were reported that suggested any potential case of severe COVID-19 among participants who received the booster dose.

Data from the safety database (non-CT)

Through 30 September 2021, 14 cases were identified among subjects who received a booster dose, and all previously received the initial 2-dose regimen of BNT162b2; 11 out of these 14 subjects were immunocompromised.

Table 54. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) [a]

<table>
<tr><td></td><td>The reported relevant PTs (> 1 occurrence) were: COVID-19 pneumonia, Drug ineffective (8 each), Dyspnoea (7), Vaccination failure (6), Acute respiratory distress syndrome, Diarrhoea (3 each). Overall, 11 cases were severe, resulting in hospitalization (10) and/or life-threatening consequences (2) or death (3). None of these 14 cases could be definitely considered VAED/VAERD.
Overall event seriousness and outcome of these 14 cases are summarized below:
<table>
<tr><th></th><th>Total Events
N = 39</th></tr>
<tr><td>Serious events*</td><td>34</td></tr>
<tr><td>Events with Criterion of Hospitalization</td><td>21</td></tr>
<tr><td colspan="2">Distribution of events by Outcome</td></tr>
<tr><td>Outcome: Death</td><td>5</td></tr>
<tr><td>Outcome: Resolved/Resolving</td><td>8</td></tr>
<tr><td>Outcome: Not resolved</td><td>20</td></tr>
<tr><td>Outcome: Resolved with sequelae</td><td>0</td></tr>
<tr><td>Outcome: Unknown/No data</td><td>7</td></tr>
<tr><td colspan="2">*In 1 case the PT Covid-19 pneumonia was made serious after the RMP DLP and the outcome of the event was changed from “unknown” to “death”.</td></tr>
</table>

<u>Conclusion:</u>
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.</td></tr>
<tr><td>Risk factors and risk groups</td><td>It is postulated that the potential risk may be increased in individuals producing lower neutralizing antibody titers or in those demonstrating waning immunity. [98]</td></tr>
</table>

Table 54. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) [a]

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; [86,98] that immune profile is elicited by COVID-19 mRNA vaccine in clinical and preclinical studies.[99,100]
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; Chilblains; 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).
b. Please note that CT dataset from the safety database includes only cases reporting SAEs.

SVII.3.2. Presentation of the Missing Information

Table 55. Use in Pregnancy and while Breast Feeding

Evidence source:
The safety profile of the vaccine is not yet fully 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. It is 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 are not yet fully understood but some data have suggested that pregnant women have an increased risk of severe disease and complications when affected by COVID-19. This information should be considered in the benefit-risk consideration for vaccination in pregnancy.

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 56. 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 MAH (see PART III.2 and PART III.3).

Table 57. 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 the 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 58. 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 59. 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 60. Long Term Safety Data

Evidence source: At this time, 6-month post dose 2 safety data are available for all 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 61. 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 are a critical component to the detection, assessment, understanding and mitigation of risks. Objectives of routine pharmacovigilance include 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 MAH, monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant 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 MAH, 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.
  - potential multisystem inflammatory syndrome in children and adults (MIS-C/A) experienced by individuals following administration of Pfizer-BioNTech COVID-19 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 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.

Bi-monthly summary safety reports

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

- Bi-monthly reports and PSURs will include results of the observed versus expected analysis for AESIs as appropriate and will present the results and details of the statistical approach.

Potential Medication Errors

This section is applicable to all formulations presented in the RMP.

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, different formulations, and 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 formulations of the COVID-19 mRNA vaccine.
- A poster with step-by-step instruction for vaccine storage, vial differentiation, 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.
- A dosing card which provides information for vaccine storage, vial differentiation, dose planning, and administration is available, which is available for healthcare provider reference.
- 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 various formulations 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.

Vial Differentiation

PBS-Sucrose formulation

- The 30 micrograms/dose concentrate for dispersion for injection vial used in individuals 12 years of age and older has a purple flip off plastic cap and label differentiation factors that indicate how to dilute it. The vial label and the SmPC includes 'Dilute Before Use' printed. If attempted to not dilute with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution, the user would only be able to extract approximately 1 dose instead of 6 doses as the filled volume is 0.45 mL.

Tris-Sucrose formulation

This drug product formulation is referred to as the 'Tris-Sucrose formulation' to emphasize the change in formulation buffer.

- The 30 micrograms/dose dispersion for injection vial used in individuals 12 years of age and older has a grey flip off plastic cap and label differentiation factors included within do not need to be diluted. The vial label and the SmPC include 'Do Not Dilute' printed. The vial label also includes a wide grey border as an additional differentiation factor. Further, if attempted to further dilute, a user would immediately experience resistance to addition of any further volume, as the filled volume is 2.25 mL and therefore, there is little remaining physical space to add additional diluent to the vial.

- The 10 micrograms/dose concentrate for dispersion for injection vial should be used only for children 5 to 11 years of age and the 10-µg RNA dose, dilution of the vaccine with 0.9% sodium chloride for injection is required, as follows: dilute the 1.3-mL filled vial with 1.3 mL 0.9% sodium chloride for injection to provide 10 doses at 10 µg RNA / 0.2 mL Injection volume. The vial has an orange plastic cap which is different from the Comirnaty 30 micrograms/dose concentrate for dispersion for injection vial that has a purple plastic cap and from the 30 micrograms/dose dispersion for injection vial that has a grey flip off plastic cap.

Various educational resources to inform HCPs on the proper preparation and differentiation will be available.

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 MAH, 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 MAH 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 MAH, 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 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 MAH 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 MAH proposes the following 17 studies, of which 4 global, 5 in Europe only, 5 in US only, 2 in US and Canada and 1 in New Zealand. There are 6 interventional studies (C4591001, C4591007, C4591015, BNT162-01 Cohort 13, C4591024 and 1 study for vaccine interactions), 2 Low-Interventional studies (WI235284 and WI255886) and 9 non-interventional studies (8 safety and 1 effectiveness), summarised in the table below and further detailed in Table 62 and Table 63.

Study Number	Country	Interventional/ Non-Interventional	Purpose
C4591001	Global	Interventional	Safety
C4591007	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/CA	Non-Interventional	Safety
C4591022	US/CA	Non-Interventional	Safety
C4591014	US	Non-Interventional	Effectiveness[a]
WI235284	US	Low-Interventional[d]	Effectiveness[a]
WI255886	EU[b]	Low-Interventional[d]	Effectiveness[a]
BNT162-01 Cohort 13	EU	Interventional	Safety
C4591024[c] (former Safety and immunogenicity in high-risk adults)	Global	Interventional	Safety
C4591030 (Co-administration study with seasonal influenza vaccine)	NZ	Interventional	Safety

a. Vaccine effectiveness is not a safety concern.
b. United Kingdom.
c. Based on the outcome of procedures PAM-MEA-015.2 and PAM-MEA-016, and in particular based on the conclusions of the Assessment Report for the Post-Authorisation Measure MEA/015.2 and MEA/016 (EMA/CHMP/498689/2021) issued on 16 September 2021, the design of study C4591024 was agreed to satisfactorily cover the objectives initially planned for study C4591018, that is therefore removed from the list of studies
d. The study does not involve any administration of vaccine or other Pfizer products but since a specimen collection procedure is required per protocol, this qualifies this study as 'low-interventional'.

Non-Interventional Post Approval Safety Studies (8)

- The MAH proposes 8 complementary studies of real-world safety of COVID-19 mRNA vaccine that use multiple data sources and study designs. These are described in Table 62 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 4 US studies and 1 US/CA 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 (C4591036).

    - 1 study will monitor rates of pregnancy and infant outcomes in planned and unplanned pregnancies exposed to BNT162b2 using an established pregnancy registry. Women receiving BNT162b2 during pregnancy will be followed from exposure to one-year post-partum. Analyses will be conducted to evaluate if the

pregnant women receiving the vaccine during pregnancy experience increased risk of pregnancy and infant outcomes compared with 1) pregnant women who are unvaccinated and 2) pregnant women who have received an influenza or tetanus, diphtheria, and acellular pertussis (Tdap) vaccine during pregnancy (C4591022).

- The protocols for the safety studies in the US (C4591009, C4591011, C4591012 and C4591022) 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 that include paediatric subjects aged 5 to < 12 years old

Studies C4591021(EU), C4591038 (former C4591021 substudy) (EU), C4591009 (US) C4591011 (US) and C4591036 (US and Canada) will assess the use of vaccine for the occurrence of safety events of interest, including myocarditis and pericarditis. Each of these

studies includes individuals of all ages, including ages 5 to <12, except for study C4591036, which only includes individuals <21 years of age.

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 5 of the real-world safety studies (C4591009, C4591010, C4591011, C4591021 [former ACCESS/VAC4EU] and C4591022), described in Table 62. 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. The MAH 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 62 and Table 63).

The MAH 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 MAH, 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.

The purpose of the original study C4591014 (a test-negative design) was further developed with 2 new vaccine effectiveness epidemiology studies not sponsored by Pfizer (WI235284 and WI255886) 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 62. 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	Any time
					CSR submission 6 months post Dose 2	31-May-2021
					Final CSR submission with supplemental follow-up	31-Dec-2023
C4591007 Global	A phase 1, open-label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA vaccine candidate against	The objective of the study is to evaluate the safety, tolerability, immunogenicity, and efficacy of the BNT162b2 RNA-based COVID-19 vaccine candidate against COVID-19 in healthy children.	Phase 1/2/3 study will evaluate up to 3 dose levels of BNT162b2 in up to 3 age groups (participants ≥ 5 to <12 years, ≥ 2 to <5 years, and ≥ 6 months to <2 years of age) for safety, tolerability, immunogenicity, and efficacy	Healthy paediatric subjects and young adults.	Final CSR submission	31-Jul-2024

Table 62. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
	COVID-19 in healthy children and young adults. Interventional *Ongoing*					
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 (all ages), pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System. This study will include an analysis of individuals who receive a booster dose of the Pfizer-BioNTech COVID-19 vaccine.	Protocol submission Protocol amendment submission (booster dose)	31-Aug-2021 31-Dec-2021
					Monitoring report submission	31-Oct-2022
					Interim Analysis submission	31-Oct-2023
					Final CSR submission	31-Oct-2025
C4591011 US	Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense population following Emergency Use Authorization.	To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, including myocarditis and pericarditis	Secondary use of real-world data to conduct comparative analyses using self-controlled risk interval and active comparator approaches. The	Department of Defense military and civilian personnel and their families (all ages) in the Military Health System.	Interim reports submission	30-Sep-2022
						31-Dec-2022
					Final CSR submission	31-Dec-2023

Table 62. 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*	following receipt of the COVID-19 mRNA vaccine.	study will conduct active surveillance of individuals who receive a booster dose of the Pfizer-BioNTech COVID-19 vaccine.			

Table 62. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
C4591012 US	Post-Emergency Use Authorization active 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. The study will also conduct active surveillance of individuals who receive a booster dose of the Pfizer-BioNTech COVID-19 vaccine.	US Veterans	Interim reports submission	30-Jun-2021
						31-Dec-2021
						30-Jun-2022
						31-Dec-2022
					Protocol amendment submission (booster dose)	30-Nov-2021
					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. Non-Interventional	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	Primary data collection cohort study This study will also conduct active surveillance of individuals who receive a booster dose of the Pfizer-	EU general population.	Final CSR submission	30-Sep-2024

Table 62. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
	Ongoing	rates elevated relative to estimated expected rates.	BioNTech COVID-19 vaccine.			

Table 62. 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 62. 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). *Ongoing*	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 62. 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
C4591024 (former Safety and	A Phase 2b, open-label study to evaluate the	Safety, tolerability and immunogenicity based on	Open uncontrolled.	High risk individuals including frail, those	Final CSR submission:	30-Jun-2023[9]

[9] Milestones for study 1024 is changed in order to reflect the revised design agreed in procedure PAM-MEA-016; in addition, according to the Assessment Report for PAM-MEA-015.2, the design of study C4591024 was agreed to satisfactorily cover the objectives initially planned for study C4591018, that is removed from the list of studies

Table 62. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
immunogenicity in high-risk adults) Global	safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age. Interventional *Ongoing*	representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal disease).		having autoimmune disease, chronic renal disease and immunocompromising conditions.		
C4591021 (former ACCESS/VAC4EU) EU	Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech.	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	Secondary database analysis of observational data to assess potential increased risk of adverse events of special interest (AESI and other clinically significant events among	EU General population (all ages).	Protocol amendment submission (booster dose):	31-Dec-2021

Table 62. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
	Coronavirus Disease 2019 (COVID-19) vaccine. Non-Interventional *Ongoing*	dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.	COVID-19 vaccine recipients in the EU. This study will include an analysis of individuals who receive booster dose of the Pfizer-BioNTech COVID-19 vaccine.		Final CSR submission:	30-Sep-2024[10]
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 investigate natural history of post-vaccination myocarditis and pericarditis. Non-Interventional *Planned*	Assessment of 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	Secondary database analysis of observational data. This study will include an analysis of individuals who receive booster dose of the Pfizer-BioNTech COVID-19 vaccine.	EU General population (all ages): individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine.	Final protocol submission	31-Jan-2022
					Final CSR submission:	30-Sep-2024

[10] 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 62. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
		vaccinated with a COVID-19 vaccine.				

Table 62. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
C4591022 US/Canada	Pfizer-BioNTech COVID-19 Vaccine exposure during pregnancy: A non-interventional post-approval safety study of pregnancy and infant outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry. Non interventional *Ongoing*	To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age.	Analyses will be conducted to evaluate if the pregnant women receiving the vaccine during pregnancy experience increased risk of pregnancy and infant outcomes compared with 1) pregnant women who are unvaccinated and 2) pregnant women who have received an influenza or tetanus, diphtheria, and acellular pertussis (Tdap) vaccine during pregnancy	Pregnant women and infant outcomes	Interim reports submission: Final CSR submission:	31-Jan-2022 31-Jan-2023 31-Jan-2024 31-Dec-2024
C4591036 (former Pediatric Heart Network Study) US/Canada	Safety surveillance study of myocarditis and myopericarditis temporally associated with Tozinameran	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. This study will include an analysis of individuals who receive booster dose of the Pfizer-BioNTech COVID-19 vaccine.	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 Final CSR submission:	30-Nov-2021 31-Oct-2025

Table 62. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
	(Comirnaty®) in persons < 21 years of age. Non-Interventional *Planned*					
C4591030 (Co-administration study with seasonal influenza vaccine) NZ	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 Final CSR submission:	17-Aug-2021[11] 31-Dec-2022

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

[11] Effettive Submission date

III.3. Summary Table of Additional Pharmacovigilance Activities

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

Table 63. 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-Dec-2023
C4591007 *Ongoing*	Global	The purpose of the dose-finding/selected-dose study is to rapidly describe the safety, tolerability, immunogenicity, and efficacy of the BNT162b2 RNA-based COVID-19 vaccine candidate against COVID-19 in healthy children.	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long term safety data.	Final CSR submission	31-Jul-2024

Table 63. 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 pregnancy Use in immunocompromised patients Use in persons with a prior history of COVID-19.	Protocol submission	31-Aug-2021
				Monitoring report submission	31-Oct-2022
				Interim Analysis submission	31-Oct-2023
				Final CSR submission	31-Oct-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.	Interim reports submission	30-Sep-2022
					31-Dec-2022

Table 63. 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
			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	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 receipt of the COVID-19 mRNA vaccine.	Myocarditis and pericarditis Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in immunocompromised patients.	Interim reports submission	30-Jun-2021 31-Dec-2021 30-Jun-2022 31-Dec-2022

Table 63. 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**
			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	31-Dec-2023

Table 63. 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 *Ongoing*	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
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 *Ongoing*	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

Table 63. 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
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
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	30-Sep-2021
				Final CSR submission	31-Dec-2022
C4591024 (former Safety and immunogenicity in high-risk adults) *Ongoing*	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	30-Jun-2021
				Final CSR submission	30-Jun-2023[9]

Table 63. 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-Jan-2022
				Final CSR submission	30-Sep-2024

Table 63. 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
C4591022 *Ongoing*	US/CA	To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age.	Use in pregnancy.	Interim reports submission	31-Jan-2022 31-Jan-2023 31-Jan-2024
				Final CSR submission	31-Dec-2024
C4591036 (former Pediatric Heart Network Study) *Planned*	US/CA	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.	Myocarditis/pericarditis Long term safety data.	Protocol submission	30-Nov-2021
				Final CSR submission	31-Oct-2025
C4591030 (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	17 Aug 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 MAH at this time. The proposed minimisation measures are summarised in the table below for each safety concern.

Table 64. 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.
M**yocarditis 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 64. 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 64. 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 65. 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 66. 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-Dec-2023) • C4591007 (31-Jul-2024) • C4591009 (31-Oct-2025) • C4591010 (30-Sep-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023)

Table 66. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		• C4591021 (former ACCESS/VAC4EU) 30-Sep-2024).
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-Dec-2023) • C4591007 (31-Jul-2024) • C4591009 (31-Oct-2025) • C4591011[b] (31-Dec-2023) • C4591012[b] (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) (30 Sep-2024)[b].

Table 66. 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). • C4591022 (31-Dec-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) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) • C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)[9]
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-Dec-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) (30-Jun-2023)[9]

Table 66. 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) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) • C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)[9]
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: • C4591030 (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-Dec-2023) • C4591007 (31-Jul-2024) • 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, C4591021 (former ACCESS/VAC4EU) and C4591022 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 5 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 67. 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 68. 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	• C4591001 • C4591007 • 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 69. 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: DHCP letter and communication plan
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 70. 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	• C4591001 • C4591007 • 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 71. 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	• C4591009[a] • C4591010[a] • C4591011[a] • C4591015 • C4591021 (former ACCESS/VAC4EU)[a] • C4591022[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, C4591021 (former ACCESS/VAC4EU) and C4591022 address only "Use in pregnancy".

Table 72. 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	• BNT162-01 cohort 13 • C4591010[a] • 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.

a. Addresses AESI-based safety events of interest

Table 73. 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	• 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 74. 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	• 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 75. 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	• C4591030 (Co-administration study with seasonal influenza vaccine) See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 76. 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	• C4591001 • C4591007 • 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.
C4591007	To assess the safety, tolerability, immunogenicity, and efficacy of the BNT162b2 RNA-based COVID-19 vaccine candidate against COVID-19 in healthy paediatric subjects.

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 (all ages), 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 (all ages) 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.

Study	Purpose of the study
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.
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.
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) among individuals (all ages) 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 (all ages) vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine.
C4591022	To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age.
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
C4591030 (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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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

Follow-up forms

Pfizer-BioNTech COVID-19 Vaccine Anaphylactic Reaction Data Capture Aid

Pfizer-BioNTech COVID-19 Vaccine VAED Data Capture Aid

Pfizer-BioNTech COVID-19 Vaccine Multisystem Inflammatory Syndrome in Pediatric and Adults (MIS-C/A) Data Capture Aid

Pfizer-BioNTech COVID-19 Vaccine Anaphylactic Reaction Data Capture Aid

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 or Other COVID-19 Vaccine)

Dose Number	Date (dd-Mmm-yyyy)	Site of injection	Route	COVID-19 Vaccine Name	Batch/Lot number
1st					
2nd					
3rd					
4th					
5th					
6th					

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
2.0	20-Oct-2021	Updated the *Product Information* section to include row for additional doses.
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 or Other COVID-19 Vaccine)

Dose Number	Date (dd-Mmm-yyyy)	Site of injection	Route	COVID-19 Vaccine Name	Batch/Lot number
1st					
2nd					
3rd					
4th					
5th					
6th					

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
3.0	20-Oct-2021	Updated the *Product Information* section to include row for additional doses.
2.0	05-Jan-2021	Title updated to Pfizer-BioNTech COVID-19 Vaccine VAED
1.0	07-Dec-2020	New DCA

Pfizer-BioNTech COVID-19 Vaccine Multisystem Inflammatory Syndrome in Pediatric and Adults (MIS-C/A) Data Capture Aid

Instructions for use:

This Data Capture Aid (DCA) is intended to enable the retrieval of clinical observations and laboratory/diagnostic test about potential MIS-C/A experienced by individuals following administration of Pfizer-BioNTech COVID-19 Vaccine. Select questions as appropriate to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term(s) 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

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 or Other COVID-19 Vaccine)

Dose Number	Date (dd-Mmm-yyyy)	Site of injection	Route	COVID-19 Vaccine Name	Batch/Lot number
1st					
2nd					
3rd					
4th					

2. Alternative causes for reported symptoms? e.g. other infectious, inflammatory, allergic or reactive etiology?
Please provide details

3. FEVER:

Measured temperature: Celsius: Fahrenheit:

Duration of fever (eg. 3 days):

4. CLINICAL MANIFESTATION

Mucocutaneous (Rash, erythema/cracking of lips, mouth, pharynx, bilateral non-exudative conjunctivitis, rash/erythema/edema of hands or feet)

If any of them: YES, please provide details: _____

Gastrointestinal (abdominal pain, vomiting, diarrhea)

If any of them: YES, please provide details: _____

Shock or hypotension?

If any of them: YES, please provide details: _____

Neurological signs/symptoms (altered mental status, headache, weakness, dizziness, paresthesia, lethargy)

If any of them: YES, please provide details: _____

Hearth failure or physical signs/symptoms of heart failure (gallop rhythm, rales, lower extremity edema, jugular venous distension, hepatosplenomegaly)

If any of them: YES, please provide details: _____

5. Are relevant lab values available?

Please indicate if the patient had any lab value abnormalities.

				If YES, please provide data			
Lab Test	Not done	No	Yes	**Date (dd-Mmm-yyyy)**	**Value**	**Reference Range**	**Unit**
C-reactive protein (CRP)	☐	☐	☐				
Erythrocyte Sedimentation Rate (ESR)	☐	☐	☐				
Ferritin	☐	☐	☐				
Procalcitonin	☐	☐	☐				
BNP (B-type natriuretic peptide)	☐	☐	☐				
NT-proBNP	☐	☐	☐				
Troponin	☐	☐	☐				
Neutrophils	☐	☐	☐				
Lymphocytes	☐	☐	☐				
Platelets	☐	☐	☐				
Other	☐	☐	☐				

6.Were any relevant additional diagnostic evaluations performed?

				If YES, please provide data	
Diagnostic evaluation	Not done	No	Yes	**Date (dd-Mmm-yyyy)**	**Result**
Echocardiogram	☐	☐	☐		
EKG (electrocardiogram)	☐	☐	☐		

7. SARS-COV-2/COVID-19 HISTORY?

				If YES, please provide data	
Exposure	Unknown	No	Yes	**Date (dd-Mmm-yyyy)**	**Result**
Laboratory-confirmed SARS-CoV-2 infection	☐	☐	☐		
Personal history of suspected COVID-19 within 12 weeks	☐	☐	☐		
Close contact with known COVID-19 case within 12 weeks	☐	☐	☐		
SARS-CoV-2 Vaccination	☐	☐	☐		

8. Did the patient receive any treatment for the MIS?

Drug	Dose & schedule	Route of administration	Indication	Date first administration (dd-Mmm-yyyy)	Date last administration (dd-Mmm-yyyy)

9. Did the patient receive concomitant medications within 2 weeks of event onset?

Drug	Dose & schedule	Route of administration	Indication	Date first administration (dd-Mmm-yyyy)	Date last administration (dd-Mmm-yyyy)

Revision History

Revision	Effective Date	Summary of Revisions
1.0	20-Dec-2021	New DCA

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

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

COVID-19 mRNA Vaccines Comirnaty and Spikevax: risk of myocarditis and pericarditis

Dear Healthcare professional,

BIONTECH/PFIZER and MODERNA BIOTECH SPAIN, S.L. in agreement with the European Medicines Agency and <National competent authority> would like to inform you of the following:

Summary

- Cases of myocarditis and pericarditis have been reported very rarely following vaccination with the COVID-19 mRNA Vaccines Comirnaty and Spikevax.
- The cases primarily occurred within 14 days after vaccination, more often after the second dose and in younger men.
- Available data suggest that the course of myocarditis and pericarditis following vaccination is similar to the course of myocarditis and pericarditis in general.
- Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis.
- Healthcare professionals should advise vaccinated individuals to seek immediate medical attention should they experience chest pain, shortness of breath, or palpitations.

Background on the safety concern

The COVID-19 mRNA vaccines, Comirnaty and Spikevax, have been approved in the EU under conditional marketing authorisation for active immunisation to prevent COVID-19 infection caused by SARS-CoV-2, in individuals 12 years of age and older (Comirnaty) and 18 years of age and older (Spikevax), respectively.

Myocarditis and pericarditis have been reported in association with the COVID-19 mRNA vaccines.

The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has evaluated all available data and concluded that a causal association between COVID-19 mRNA vaccines and myocarditis and pericarditis is at least a reasonable possibility. Accordingly, the Summary of Product Characteristics, sections 4.4 (‘Special warnings and precautions for use’) and 4.8 (‘Undesirable effects’) have been updated.

The benefits of vaccination continue to outweigh any risks.

Up to 31 May 2021 in the EEA, 145 cases of myocarditis occurred among people who received Comirnaty and 19 cases among people who received Spikevax. In addition, 138 cases of pericarditis occurred following the use of Comirnaty and 19 cases following the use of Spikevax.

It is estimated that around 177 million doses of Comirnaty and 20 million doses of Spikevax have been administered in the EEA up to 31 May 2021.

Call for reporting

Healthcare professionals are asked to report any suspected adverse reactions via their national reporting system and include batch/Lot number if available.

These medicinal products are subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Marketing Authorisation Holders' contact points

MODERNA BIOTECH SPAIN, S.L. Calle Monte Esquinza 30 28010 Madrid Spain medinfo@modernatx.com https://www.modernacovid19global.com/	BioNTech Manufacturing GmbH An der Goldgrube 12 55131 Mainz Germany medinfo@biontech.de www.comirnatyglobal.com

The DHPC distribution started on 19 July 2021 in all EEA countries as per the EMA's communication plan.