COMIRNATY, COMIRNATY ORIGINAL/OMICRON BA.1, COMIRNATY ORIGINAL/OMICRON BA.4-5, COMIRNATY OMICRON XBB.1.5

(COVID-19 mRNA VACCINE) RISK MANAGEMENT PLAN

RMP Version number: 13.0

Data lock point for this RMP, see below:

Age group[a]	Module SIII. Clinical Trial Exposure	Module SVII.3. Details of Important Risks
Monovalent Omicron XBB.1.5		
Individuals: 6 months to <5 years of age 5 to 11 years of age 12 years of age and older	N/A	15 November 2023 Pfizer safety database (non-CT dataset) Stratified by product, age group and without booster doses counted
bivalent BNT162b2 (original/Omi BA.1 and BA.4/BA.5)		
Individuals: 6 months to <5 years of age 5 to 11 years of age 12 years of age and older	N/A	15 November 2023 Pfizer safety database (non-CT dataset) Stratified by product, age group and without booster doses counted
Comirnaty original (monovalent)		
Individuals : 6 months to <5 years of age 5 to 11 years of age 12 years of age and older	N/A	15 November 2023 Pfizer safety database (non-CT dataset) Stratified by product, age group and without booster doses counted
bivalent BNT162b2 (original/Omi BA.4/BA.5)		
12 years of age and older bivalent BNT162b2 (original/Omi BA.4/BA.5) modified vaccine (BNT162b2 + BNT162b2 OMI 30 µg) as primary series or 4th dose	12 October 2022 Cohort 2 31 Oct 2022 Cohort 3 Study C4591044	12 October 2022 Cohort 2 31 Oct 2022 Cohort 3 Pfizer Clinical Database - Study C4591044
5-<12 years of age bivalent BNT162b2 (original/Omi BA.4/BA.5) modified vaccine (BNT162b2 + BNT162b2 OMI 10 µg) as 4th dose	25 November 2022 [C4591048 Substudy D (group 2)]	25 November 2022 Pfizer Clinical Database - Study C4591048 (SSD group 2)
6 months to <5 years of age bivalent BNT162b2 (original/Omi BA.4/BA.5) modified vaccine (BNT162b2 + BNT162b2 OMI 3 µg) as 4th dose	25 November 2022 [C4591048 Substudy B, (group 2)]	25 November 2022 Pfizer Clinical Database - Study C4591048 (SSB group 2)
Comirnaty original (monovalent) + bivalent BNT162b2 (original/Omi BA.1)		
12 years of age and older booster dose of a bivalent BNT162b2 (original/Omi BA.1) modified vaccine (BNT162b2 + BNT162b2 OMI 30 µg)	Sentinel cohort 05 April 2022 and expanded cohort cut-off date: 16 May 2022 C4591031 (Substudy E).	Sentinel cohort 05 April 2022 and expanded cohort cut-off date: 16 May 2022 Pfizer Clinical Database - Study C4591031 (Substudy E).

	11 March 2022 C4591031 (Substudy D – Cohort 2)	11 March 2022 Pfizer Clinical Database - Study C4591031 (SSD – Cohort 2)
Comirnaty original (monovalent)		
6 months to <5 years (Primary series)	16 July 2021 (Phase 1) 29 April 2022 (Phase 2/3) 23 February 2023 (Phase 2/3, 6MPD3)	29 April 2022 Pfizer Clinical Database – Study C4591007 (Phase 2/3)
5 to <12 years of age (Primary series)	06 September 2021	06 September 2021 Pfizer Clinical Database
Booster (3rd) dose in 5 to <12 years of age	22 March 2022 (Phase 2/3)	22 March 2022 Pfizer Clinical Database Study C4591007
12-15 years of age, including severely immunocompromised (Primary series)	13 March 2021 (Pfizer Clinical Database)	30 September 2021 Pfizer Safety Database (CT dataset)
Booster (3rd) dose in 12-15 years of age (6 months post dose 3 data)	03 November 2022 (Study C4591001)	03 November 2022 Pfizer Clinical Database, Study C4591001
Booster (3rd) dose in 12-17 years of age 1 month post dose 3	14 July 2022 (C4591031 Substudy C)	
16 years and older, including severely immunocompromised (Primary series)	13 March 2021 (Pfizer Clinical Database) 23 October 2020 (BioNTech Clinical Database)	30 September 2021 Pfizer Safety Database (CT dataset)
Booster (3rd) dose in 16 years and older[b]	17 June 2021 (Study C4591001)	17 June 2021 Pfizer Clinical Database - Study C4591001
SV Post-Authorization Experience: 18 June 2023		

a. Detailed language is included in the SmPC.
b. 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: 31 May 2024

Rationale for submitting an updated RMP (v 13.0): This Type II variation includes an updated RMP (based on v 12.0) that consolidates RMP v 11.2 which included the removal of studies/milestones from aPV activities of the following studies: C4591011 (terminated) and C4591012 (completed). Additional changes to other study milestones were performed.

Summary of significant changes in the RMP version:

RMP Part/Module	RMP v 13.0 Major Changes
PART I PRODUCT(S) OVERVIEW	
	Editorial changes and inclusion of pre-filled syringe (PFS – plastic) presentation
PART II SAFETY SPECIFICATION	
PART II.Module SI Epidemiology of the Indication(s) and Target Populations	Editorial changes and new updated references related to the new strain XBB.1.5.
PART II.Module SII Non-Clinical Part of the Safety Specification	No changes made.
PART II.Module SIII Clinical Trial Exposure	Minor edits.
PART II.Module SIV Populations Not Studied in Clinical Trials	No changes made.
PART II.Module SV Post-Authorisation Experience	No changes made.
PART II.Module SVI Additional EU Requirements for the Safety Specification	No changes made.
PART II.Module SVII Identified and Potential Risks	Post Marketing data from the safety database for the important identified risk of myocarditis/pericarditis updated as of 15 Nov 2023.
PART II.Module SVIII Summary of the Safety Concerns	No changes made.
PART III PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)	
III.1 Routine Pharmacovigilance activities.	Editorial changes in Part III.1 and inclusion of pre-filled syringe – PFS (plastic) presentation.
III.2 Additional Pharmacovigilance Activities and III.3 Summary Table of Additional Pharmacovigilance Activities	Removal of study/milestones for C4591011 and C4591012 and milestone updated for studies: C4591009, C4591021, C4591022, C4591024, C4591036, C4591051, and C4591052.
PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES	
	No changes made.
PART V PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	
V.1 Routine Risk Minimisation Measures V.2 Additional Risk Minimisation Measures V.3 Summary of Risk Minimisation Measures	Updated based on the changes made in PART III.2.
PART VI PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	
I The Medicine and What It Is Used For II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks	No changes made. Updated based on the changes made in PART III and V.
PART VII PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	

RMP Part/Module	RMP v 13.0 Major Changes
Annex 2: Updated to remove studies C4591011 and C4591012 from the ongoing and planned aPV activities table and milestones updated for studies: C4591009, C4591021, C4591022, C4591024, C4591036, C4591051 and C4591052. Annex 3: Updated to reflect studies C4591011 and C4591012 completion/termination. Annex 8: Changes to reflect the updates.	

Other RMP versions under evaluation: None

Details of the currently approved RMP

RMP version number: 12.0

Approved with procedure number: EMEA/H/C/005735/II/0201

Date of approval: CHMP Opinion: 30 May 2024

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
aPV	Additional pharmacovigilance
ARDS	acute respiratory distress syndrome
BALB/c	bagg albino
BC	Brighton Collaboration
BEST	biologics effectiveness and safety
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
CP	contractual party
CRF	Case report form
CRRT	continuous renal replacement therapy
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
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
ECDC	European Center for Disease Control
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
HER	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
HCO	health care organization
HCP	health care professional
HCV	hepatitis c virus
HIV	human immunodeficiency virus
IA	interim analysis
ICU	intensive care unit
IFN	interferon
Ig E	immunoglobulin E

Abbreviation	Definition of Term
IL-4	interleukin 4
IM	intramuscular(ly)
IMD	index of multiple deprivation
IND	investigational new drug
IRR	incidence rate ratio
LAC	Los Angeles County
LNP	lipid nanoparticle
LSV	last subject visit
MAA	marketing authorization applicant
MAH	marketing authorisation holder
Mcg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome-coronavirus
MHS	Military Health System
MIS-C	multisystem inflammatory syndrome in children
mRNA	messenger ribonucleic acid
modRNA	nucleoside-modified messenger ribonucleic acid
NCMD	national child mortality database
NCHS	national center for health statistics
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
OMI	Omicron
PASS	post-authorisation safety study
PBS	Phosphate Buffered Saline
PC	product complaint
PCR	polymerase chain reaction
PD1, PD2, PD3	post dose 1, post dose 2, post dose 3
PK	Pharmacokinetic
PHN	Pediatric Heart Network
PRAC	Pharmacovigilance risk assessment committee
PSUR	periodic safety update report
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
SIIV	seasonal inactivated influenza vaccine
SMQ	standardised MedDRA query
SmPC	summary of product characteristics
SMSR	summary monthly safety report
SPEAC	Safety Platform for Emergency vACcines

Abbreviation	Definition of Term
SSR	summary safety report
SSE	substudy E
Tdap	tetanus, diphtheria, and acellular pertussis
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
TRIS	Tromethamine Buffer or (HOCH2)3CNH
UK	United Kingdom
US	United States
V8	variant 8
V9	variant 9
VAC4EU	Vaccine monitoring Collaboration for Europe
VAED	vaccine-associated enhanced disease
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VAERD	vaccine-associated enhanced respiratory disease
VSD	Vaccine Safety Datalink
WBC	white blood cells
WHO	World Health Organization
WOCBP	women of child-bearing potential
WT	Wild type

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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 (Original). Riltozinameran is a 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 (Omicron BA.1). Famtozinameran is a 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 (Omicron BA.4-5). Raxtozinameran is a 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 (Omicron XBB.1.5).
Pharmacotherapeutic group(s) (ATC Code)	J07BN01
Marketing Authorisation Holder	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:	<u>Chemical class</u> Nucleoside-modified messenger RNA is formulated in LNP
	<u>Summary of mode of action</u> 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.
	<u>Important information about its composition</u> **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 injection sodium hydroxide (for pH adjustment) hydrochloric acid (for pH adjustment) **Excipients for 30 micrograms/dose dispersion for injection (Tris-Sucrose):** ALC-0315 ALC-0159 DSPC cholesterol trometamol trometamol hydrochloride sucrose water for injection. **Excipients for 10 micrograms/dose concentrate for dispersion for injection, and for 3 micrograms/dose concentrate for dispersion for injection, (Tris-sucrose):** ALC-0315 ALC-0159 DSPC cholesterol trometamol trometamol hydrochloride sucrose water for injection **Comirnaty Original/Omicron BA.1:** **Excipients for 15/15 micrograms/dose dispersion for injection (Tris-sucrose):** ALC-0315 ALC-0159 DSPC cholesterol trometamol trometamol hydrochloride sucrose water for injection **Comirnaty Original/Omicron BA.4-5:** **Excipients for 15/15, 5/5 and 1.5/1.5 micrograms/dose dispersion for injection (Tris-sucrose):** ALC-0315 ALC-0159 DSPC cholesterol trometamol trometamol hydrochloride sucrose water for injection

	Comirnaty Omicron XBB.1.5: ((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 Trometamol Trometamol hydrochloride Sucrose Water for injections
Hyperlink to the Product Information:	Please refer to Module 1.3.1 of this submission
Indication in the EEA	Comirnaty and Comirnaty Original/Omicron BA.4-5 are indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 6 months of age and older. Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older. Comirnaty Omicron XBB.1.5 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 6 months of age and older.
Dosage in the EEA	**Comirnaty PBS-Sucrose (30 micrograms/dose)** *Individuals 12 years of age and older* Comirnaty is administered intramuscularly after dilution as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Severely immunocompromised aged 12 years and older* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. *Elderly population* No dose adjustment is required in elderly individuals ≥ 65 years of age. **Comirnaty Tris-sucrose (30 micrograms/dose)** *Individuals 12 years of age and older* Comirnaty is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Severely immunocompromised aged 12 years and older* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. *Elderly population* No dose adjustment is required in elderly individuals ≥ 65 years of age.

	Comirnaty Tris-sucrose (10 micrograms/dose) *Children 5 to 11 years (i.e., 5 to less than 12 years of age)* Comirnaty 10 micrograms/dose is administered intramuscularly after dilution as a single dose of 0.2 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty 10 micrograms/dose should be administered at least 3 months after the most recent dose of a COVID 19 vaccine. *Severely immunocompromised aged 5 years and older* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. **Comirnaty Tris-sucrose (3 micrograms/dose)** *Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS CoV-2 infection* Comirnaty 3 micrograms/dose is administered intramuscularly after dilution as a single dose of 0.2 mL for infants and children 6 months to 4 years of age. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Infants and children 6 months to 4 years of age without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection* Comirnaty (3 mcg)/dose is administered intramuscularly after dilution, as a primary course of 3 doses (0.2 mL each). It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose. If a child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level. *Severely immunocompromised aged 6 months to 4 years* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. *Interchangeability* The primary course may consist of either Comirnaty or Comirnaty Original/Omicron BA.4-5 (or a combination of both) but not exceeding the total number of doses required as primary course. The primary course should only be administered once. The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers to complete the primary course has not been established. **Comirnaty Original/Omicron BA.1 Tris-sucrose (15/15 micrograms/dose)** *Individuals 12 years of age and older* Comirnaty Original/Omicron BA.1 is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status.

	For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Severely immunocompromised aged 12 years and older* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. *Elderly population* No dose adjustment is required in elderly individuals ≥ 65 years of age. **Comirnaty Original/Omicron BA.4-5 Tris-sucrose (15/15 micrograms/dose)** *Individuals 12 years of age and older* Comirnaty Original/Omicron BA.4-5 is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Severely immunocompromised aged 12 years and older* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations . *Elderly population* No dose adjustment is required in elderly individuals ≥ 65 years of age **Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose (Orange cap)** *Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)* Comirnaty Original/Omicron BA.4-5 is administered intramuscularly after dilution as a single dose of 0.2 mL for individuals 5 to 11 years of age regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Severely immunocompromised aged 5 years and older* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. **Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose (Blue cap)** *Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)* Comirnaty Original/Omicron BA.4-5 is administered intramuscularly as a single dose of 0.2 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Severely immunocompromised aged 5 years and older*

	Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. **Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose** *Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS CoV-2 infection* Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms/dose) is administered intramuscularly after dilution as a single dose of 0.2 mL for infants and children 6 months to 4 years of age. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms/dose) should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Infants and children aged 6 months to 4 years without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection* Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose is administered intramuscularly after dilution as a primary course of 3 doses (0.2 mL each). It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose. If a child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms or 1.5/1.5 micrograms dose level. *Severely immunocompromised aged 6 months to 4 years* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. *Interchangeability* The primary course may consist of either Comirnaty or Comirnaty Original/Omicron BA.4-5 (or a combination of both) but not exceeding the total number of doses required as primary course. The primary course should only be administered once. Individuals who have received a dose of Comirnaty should continue to receive Comirnaty or receive Comirnaty Original/Omicron BA.4-5 to complete the primary course. Individuals who have received a dose of Comirnaty Original/Omicron BA.4-5 should receive Comirnaty Original/Omicron BA.4-5 to complete the primary course. The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers to complete the primary course has not been established. **Comirnaty Omicron XBB.1.5 (30 micrograms)/dose** *Individuals 12 years of age and older*

	Comirnaty Omicron XBB.1.5 (30 micrograms)/dose is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Severely immunocompromised aged 12 years and older* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. *Elderly population* No dose adjustment is required in elderly individuals ≥ 65 years of age. **Comirnaty Omicron XBB.1.5 (10 micrograms)/dose** *Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)* Comirnaty Omicron XBB.1.5 (10 micrograms)/ dose concentrate for dispersion for injection is administered intramuscularly after dilution as a single dose of 0.2 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status. Comirnaty Omicron XBB.1.5 Original (10 micrograms) /dose dispersion for injection is administered intramuscularly as a single dose of 0.3 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Severely immunocompromised aged 5 years and older* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. **Comirnaty Omicron XBB.1.5 (3 micrograms)/dose** *Infants and children 6 months to 4 years of age without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection* Comirnaty Omicron XBB.1.5 (3 micrograms)/dose is administered intramuscularly after dilution as a primary course of 3 doses (0.2 mL each). It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose. If a child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level. *Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS CoV-2 infection*

	Comirnaty Omicron XBB.1.5 (3 micrograms)/dose is administered intramuscularly after dilution as a single dose of 0.2 mL for infants and children 6 months to 4 years of age. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Severely immunocompromised aged 6 months to 4 years* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. *Interchangeability* The primary course may consist of either Comirnaty, Comirnaty Original/Omicron BA.4-5, or Comirnaty Omicron XBB.1.5 (or a combination) but not exceeding the total number of doses required as primary course. The primary course should only be administered once. The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers has not been established.
Pharmaceutical form and strengths	**PBS-Sucrose (Comirnaty)** *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 **Tris-sucrose (Comirnaty)** *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. *Infants and children 6 months to 4 years* 3 micrograms/dose concentrate for dispersion for injection (Maroon cap). After dilution, each vial contains 10 doses of 0.2 mL. **Tris-sucrose (Comirnaty Original/Omicron BA.1)** *Individuals 12 years of age and older* 15/15 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. **Tris-sucrose (Comirnaty Original/Omicron BA.4-5)** *Individuals 12 years of age and older* 15/15 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 of age (i.e., 5 to less than 12 years of age)* 5/5 micrograms/dose concentrate for dispersion for injection (Orange cap). After dilution each vial contains 10 doses of 0.2 mL. 5/5 micrograms/dose for dispersion for injection (Blue cap). The drug product does not require dilution for administration. One single dose vial contains 1 dose of 0.3 mL (Light blue cap). One multidose vial (2.25 mL) contains 6 doses of 0.3 mL (Dark blue cap) *Infants and children aged 6 months to 4 years* 1.5/1.5 micrograms/dose concentrate for dispersion for injection (Maroon cap). After dilution each vial contains 10 doses of 0.2 mL. **Tris-sucrose (Comirnaty Omicron XBB.1.5)** *Individuals 12 years of age and older* 30 micrograms/dose dispersion for injection (Grey cap) - Single dose: each vial contains 1 dose of 0.3 mL - Multidose vials: each vial contains 6 doses of 0.3 mL The drug product does not require dilution for administration. 30 micrograms/dose dispersion for injection in pre-filled syringe - One single dose pre-filled syringe contains 1 dose of 0.3 mL *Children 5 to 11 years of age (i.e., 5 to less than 12 years of age)* 10 micrograms/dose concentrate for dispersion for injection (Orange cap) After dilution, each vials contain 10 doses of 0.2 mL 10 micrograms/dose dispersion for injection (Blue cap) - Single dose: each vial contains 1 dose of 0.3 mL - Multidose vials: each vial contains 6 doses of 0.3 mL The drug product does not require dilution for administration. *Infants and children aged 6 months to 4 years* 3 micrograms/dose concentrate for dispersion for injection (Maroon cap). After dilution, each vial contains 10 doses of 0.2 mL of vaccine.
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 6 months of age and older (Comirnaty Original, Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5)
- individuals 12 years of age and older (Comirnaty Original/Omicron BA.1)

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 organization that collects COVID-19 data from official reports and publishes current global and country specific statistics online.[3]

As of 23 November 2023, the overall number of people who had been infected with SARS-CoV-2 was over 698 million worldwide.[4] Table 1 shows the incidence and prevalence as of 23 November 2023 for the US, UK, and EU-27 countries. In the EU and the UK, by 23 November 2023 the total number of confirmed cases had accumulated to 211 million, or 414, 893 per 1,000,000 people. Across 27 countries in the EU, the number of confirmed cases ranged from 173,694 to 670,727 cases per 1,000,000 people. Romania and Poland reported the lowest incidence rates while France, Slovenia, and Austria reported the highest.[4]

In the US, the number of confirmed cases had reached over 109 million cases by 23 November 2023.[4]

Table 1. Incidence, Prevalence, and Mortality of COVID-19 as of 23 November 2023

	Total Cases	Incidence: Total Cases/ 1,000,000	Active Cases	Prevalence: Active Cases/ 1,000,000	Total Deaths	Mortality: Deaths / 1,000,000	Population
Global	698,133,258	89,564	21,589,327	26,738	6,941,840	890.6	8,074,548,806[a]
EU-27	186,229,536	423,094	475,879	1,081	1,247,613	2,834	440,161,068
UK	24,809,742	362,197	10,131	148	231,692	3,382	68,497,907
EU-27 + UK	211,039,278	414,893	486,010	955	1,479,305	2,908	508,658,975
US	109,475,371	326,982	919,833	2,747	1,183,227	3,534	334,805,269
EU-27 Countries							
Austria	6,081,287	670,727	3,811	420	22,542	2,486	9,066,710
Belgium	4,829,921	413,936	6,256	536	34,376	2,946	11,668,278
Bulgaria	1,327,375	193,930	644	94	38,608	5,641	6,844,597
Croatia	1,277,094	314,611	347	85	18,495	4,556	4,059,286
Cyprus	660,854	540,184	0	-	1,364	1,115	1,223,387
Czech Republic	4,685,890	436,433	10,433	972	43,025	4,007	10,736,784
Denmark	3,183,756	545,636	0	-	8,814	1,511	5,834,950
Estonia	622,146	470,642	N/A	71,226	3,001	2,270	1,321,910
Finland	1,499,712	269,977	7,851	1,413	10,864	1,956	5,554,960
France	40,138,560	612,013	0	-	167,642	2,556	65,584,518
Germany	38,623,319	460,439	204,841	2,442	177,878	2,121	83,883,596
Greece	6,101,379	591,412	0	-	37,089	3,595	10,316,637
Hungary	2,212,010	230,268	10,974	1,142	48,881	5,088	9,606,259
Ireland	1,724,553	343,523	1,457	290	9,346	1,862	5,020,19
Italy	26,318,717	436,733	172,099	2,856	192,909	3,201	60,262,770
Latvia	979,875	529,995	2,016	1,090	6,453	3,490	1,848,837
Lithuania	1,351,603	507,795	11,591	4,355	9,762	3,668	2,661,708
Luxembourg	319,959	498,091	N/A	3,171	1,232	1,918	642,371
Malta	120,772	271,989	432	973	866	1,950	444,033
Netherlands	8,620,051	500,832	216	13	22,992	1,336	17,211,447
Poland	6,555,173	173,694	N/A	29,133	119,753	3,173	37,739,785
Portugal	5,631,281	555,322	0	-	27,686	2,730	10,140,570
Romania	3,502,498	184,038	2,891	152	68,613	3,605	19,031,335
Slovakia	1,868,801	342,259	329	60	21,167	3,877	5,460,193
Slovenia	1,348,489	648,925	1,115	537	7,100	3,417	2,078,034
Spain	13,914,811	297,840	30,634	656	121,760	2,606	46,719,142
Sweden	2,729,650	267,116	7,942	777	25,395	2,485	10,218,971

a. "World population based on https://www.worldometers.info/world-population/#:~:text=7.9%20Billion%20(2022),Nations%20estimates%20elaborated%20by%20Worldometer. accessed on 23 November 2023"

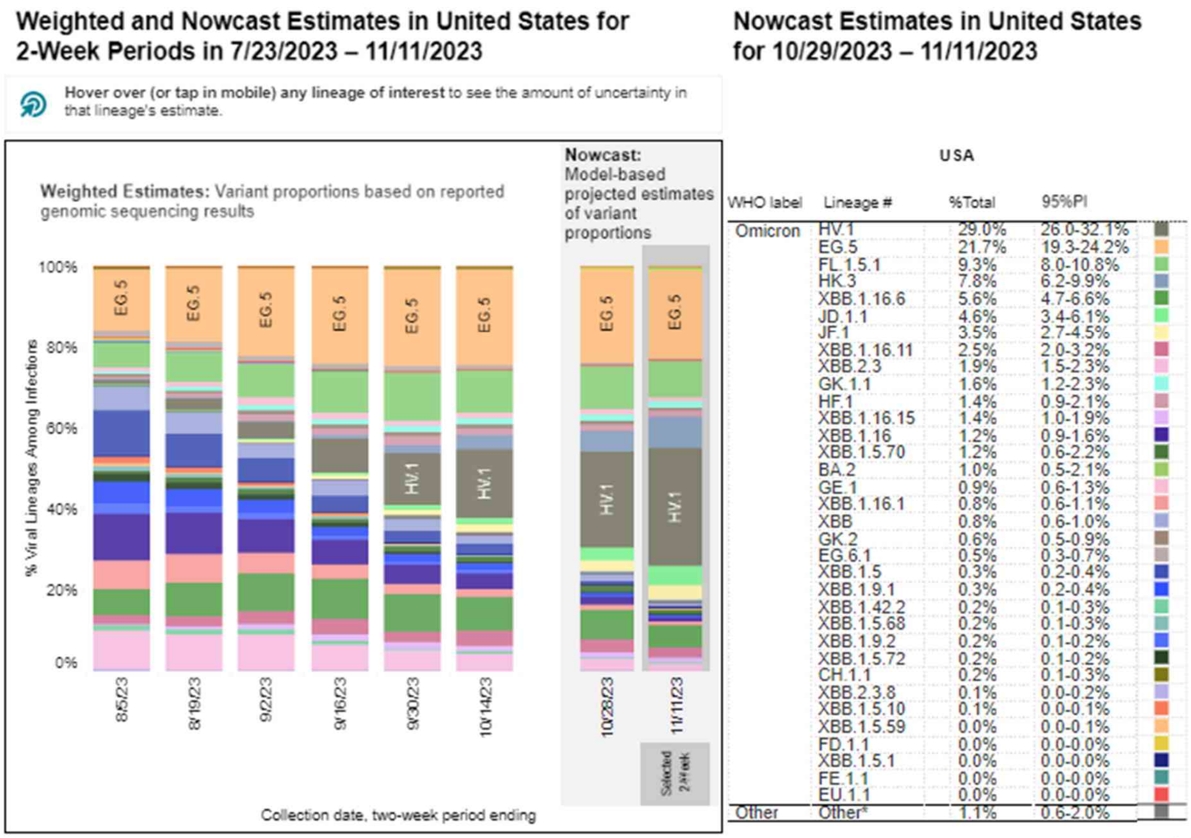
The reported numbers refer to cases that have been tested and confirmed to be carrying the virus and sometimes, depending upon the country, also presumptive, suspect, or probable cases of detected infection. There are large geographic variations in the proportion of the population tested as well as in 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.[5]

Further, as at-home rapid testing kits have become more readily available[6] and formal testing resources reach capacity due to the Omicron variant, the true estimate of cases is estimated to be larger than formally reported counts. The numbers should therefore be interpreted with caution.[7] The variants from all SARS-CoV-2 specimens sequenced by the CDC during the week ending 11 November 2023 can be found in Figure 1 below, along with the variant proportions identified from the week ending 23 July 2023 through the week ending 11 November 2023. Figure 2 shows the variant proportions of all EU-27 countries and UK from Weeks 33-48 2023.[8]

Figure 3 shows a significant decline in daily new confirmed COVID-19 cases over the period of one year in Europe i.e., from October 2022 (before identification on XBB.1.5) to

November 2023 (after identification of XBB.1.5); EU: 203,329.14 cases versus 2,271.86 cases.

Figure 1. Variant proportions for all SARS-CoV-2 specimens sequenced by the CDC during the week ending 11 November 2023 and since the week ending 23 July 2023.



USA

WHO label	Lineage #	%Total	95%PI
Omicron	HV.1	29.0%	26.0-32.1%
	EG.5	21.7%	19.3-24.2%
	FL.1.5.1	9.3%	8.0-10.8%
	HK.3	7.8%	6.2-9.9%
	XBB.1.16.6	5.6%	4.7-6.6%
	JD.1.1	4.6%	3.4-6.1%
	JF.1	3.5%	2.7-4.5%
	XBB.1.16.11	2.5%	2.0-3.2%
	XBB.2.3	1.9%	1.5-2.3%
	GK.1.1	1.6%	1.2-2.3%
	HF.1	1.4%	0.9-2.1%
	XBB.1.16.15	1.4%	1.0-1.9%
	XBB.1.16	1.2%	0.9-1.6%
	XBB.1.5.70	1.2%	0.6-2.2%
	BA.2	1.0%	0.5-2.1%
	GE.1	0.9%	0.6-1.3%
	XBB.1.16.1	0.8%	0.6-1.1%
	XBB	0.8%	0.6-1.0%
	GK.2	0.6%	0.5-0.9%
	EG.6.1	0.5%	0.3-0.7%
	XBB.1.5	0.3%	0.2-0.4%
	XBB.1.9.1	0.3%	0.2-0.4%
	XBB.1.42.2	0.2%	0.1-0.3%
	XBB.1.5.68	0.2%	0.1-0.3%
	XBB.1.9.2	0.2%	0.1-0.2%
	XBB.1.5.72	0.2%	0.1-0.2%
	CH.1.1	0.2%	0.1-0.3%
	XBB.2.3.8	0.1%	0.0-0.2%
	XBB.1.5.10	0.1%	0.0-0.1%
	XBB.1.5.59	0.0%	0.0-0.1%
	FD.1.1	0.0%	0.0-0.0%
	XBB.1.5.1	0.0%	0.0-0.0%
	FE.1.1	0.0%	0.0-0.0%
	EU.1.1	0.0%	0.0-0.0%
Other	Other*	1.1%	0.6-2.0%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one 2-week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all 2-week periods displayed.

\# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.2.75.2, CH.1.1 and BN.1, BA.2.75 sublineages are aggregated with BA.2.75. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BF.11, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Except the lineages shown and their sublineages, sublineages of XBB are aggregated to XBB. Except XBB.1.5.1,XBB.1.5.10,FD.2,EU.1.1,XBB.1.5.68 and XBB.1.5.70 sublineages of XBB.1.5 are aggregated to XBB.1.5. Except FL.1.5.1, sublineages of XBB.1.9.1 are aggregated to XBB.1.9.1. Except XBB.1.16.1,XBB.1.16.11,XBB.1.16.15 sublineages of XBB.1.16 are aggregated to XBB.1.16, sublineages of XBB.1.42.2 are aggregated to XBB. Except FE.1.1, sublineages of XBB.1.18.1 are aggregated to XBB. For all the other lineages listed, their sublineages are aggregated to the listed parental lineages respectively. Previously, FL.1.5.1, GE.1, EG.6.1 and HV.1, FD.1.1, XBB.2.3.8, HF.1, GK.2, GK.1.1, HK.3, JD.1.1, JF.1 was aggregated to XBB.1.9.1, XBB.2.3.10, XBB.1.9.2, XBB.1.5.15, XBB.2.3, XBB.1.16.13, XBB.1.5.70, XBB.1.9.2.5.1.1, XBB.1.5.102 and XBB.1.16.6 respectively. Lineages BA.2.75.2, XBB, XBB.1.5 , XBB.1.5.1, XBB.1.5.10, FD.2, XBB.1.9.1, XBB.1.9.2, XBB.1.16, XBB.1.16.1, XBB.2.3, BN.1, BA.4.6, BF.7, BF.11, BA.5.2.6 ,BQ.1.1, EU.1.1, XBB.1.5.68, FE.1.1, EG.5, XBB.1.5.72 , FL.1.5.1, GE.1, EG.6.1,XBB.1.16.11, FD.1.1, XBB.1.5.70, XBB.2.3.8, HV.1, XBB.1.42.2, GK.2, HF.1, XBB.1.16.15, GK.1.1, HK.3, JF.1 contain the spike substitution R346T.

Figure 2. SARS-CoV-2 virus characterisation using ERVISS database – weekly variant detection by country (EU-27 & United Kingdom) (Week 33-Week 48 2023)

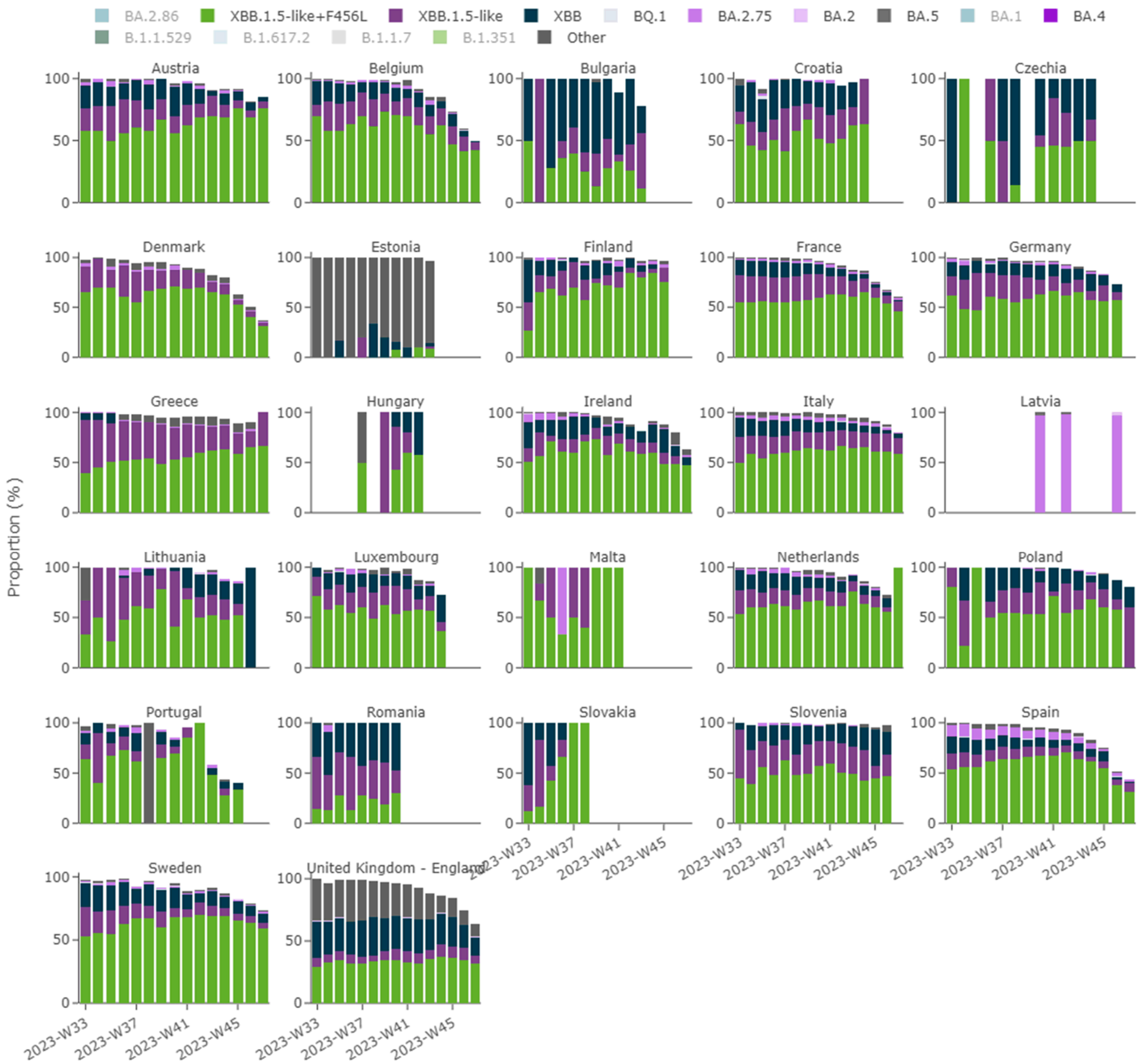
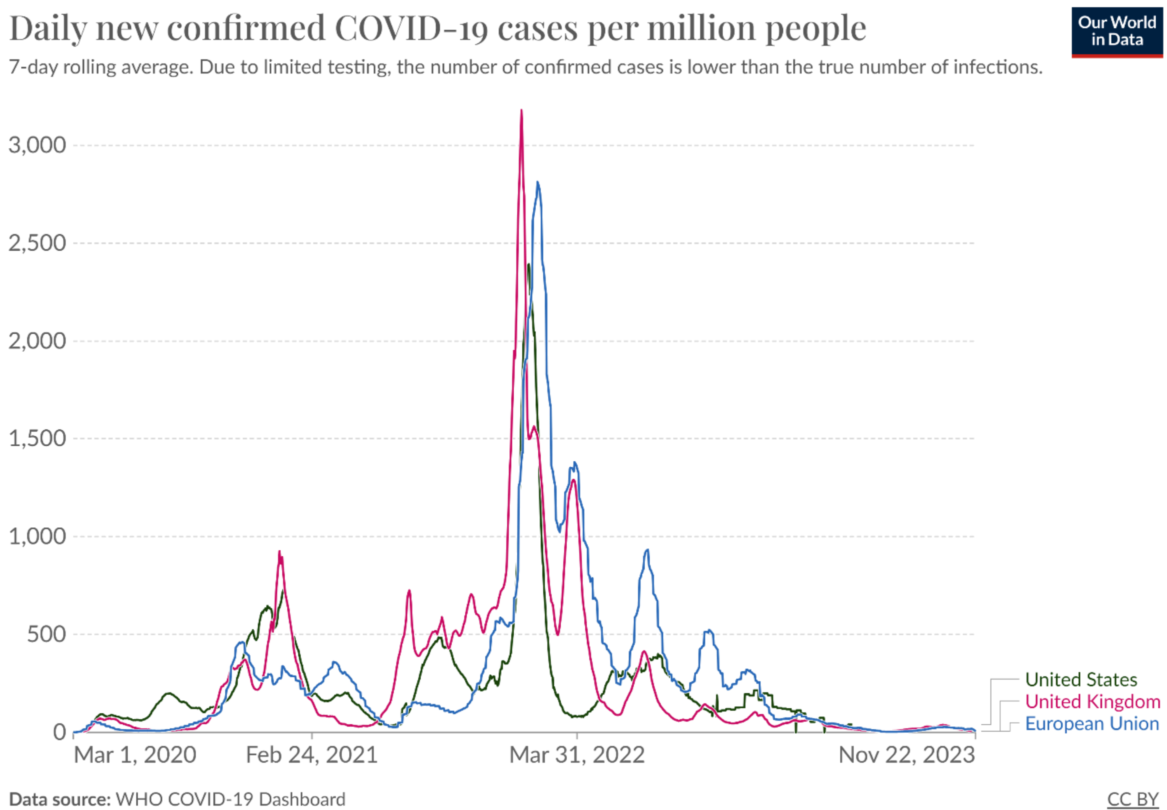


Figure 3. Daily new confirmed COVID-19 cases per million people: before & after XBB.1.5 recognition



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 22 November 2023 the overall prevalence estimates for the EU and UK were 299 and 160 active cases per 100,000, respectively.[4] The range of reported prevalence for EU-27 was 0 to 6,398 per 100,000:Greece, Slovakia and Czech Republic reported the lowest prevalence while, Luxembourg, Poland and Estonia reported the highest. It should be noted that Greece reported 0 active cases on 23 November 2023, leading to a prevalence estimate of 0 per 100,000 population.

In the US, the prevalence on 03 January 2023 was 584 active cases per 100,000[4], which was further reduced to 274 cases per 100,000[4] by 22 Nov 2023.

As of 07 May 2023,[9] XBB.1.5 had a global prevalence of 41.57 % and had been detected in 113 countries (World Health Organization 2023). As of 29 September 2023, XBB.1.5 is still considered a variant of interest and has a prevalence of 8.6 % (World Health Organization, 2023).

Omicron subvariant XBB.1.5-specific data

The derivative of Omicron subvariant BA.2 identified in recent past is known XBB.1.5. It is believed to have a mutation that can increase transmissibility of the virus by increasing cell affinity. XBB.1.5 contains 3 additional non-synonymous mutations when compared to XBB: Spike G252V (defining for XBB.1), S486P, and Orf8:G8*. Orf8:G8* is present in some XBB.1 samples but is not defining in its characterisation. In total there are 27,897 XBB.1.5 samples annotated in GISAID, with 21,128 samples uploaded by the USA (76%). XBB.1.5 has been identified in 2,157 UK samples through sequencing.[10]

Sublineage XBB.1.5 belongs to the Global Initiative on Sharing All Influenza Data (GSAID) Clade 23A and, from 22 October 2022 to 21 February 2023, a total of 45.193 Omicron XBB.1.5 variant sequences were reported from 74 countries (as per the WHO report) with a genome worldwide prevalence of about 21%. However, it should be pointed out that most of these sequences are from the USA (72.2%) and the UK (7.3%), while, as of late February 2023, other countries show a genome prevalence of no more than 20%.[11]

As reflected in the figures above, after the derivation of XBB.1.5 from its predecessor, the COVID-19 cases in the US increased from 1% to 40% with rapid transmission due to XBB.1.5. As of 13 January 2023, the CDC has now estimated that XBB.1.5 accounts for about 43% of cases.[12] However, as per recent updates in CDC COVID tracker using Nowcast system as of 13 May 2023, XBB.1.5 lineage accounted for 64% of total variants,[13] showing a rapid transmissibility of this sub-lineage.

In the northeastern US states, more than 70% of the cases are caused by XBB.1.5 whereas only 5–6% of the cases were from XBB.1.5 in the Upper Midwest US.[14] In Texas, the gateway US state to Mexico and Latin America, just under 20% of the cases were from XBB.1.5.[15,16]

Table 2 shows country-specific epidemiology data across the globe for the outbreak of COVID-19 Omicron subvariant XBB.1.5.[15]

Table 2. Country-specific epidemiology data across the globe for the outbreak of COVID-19 Omicron subvariant XBB.1.5

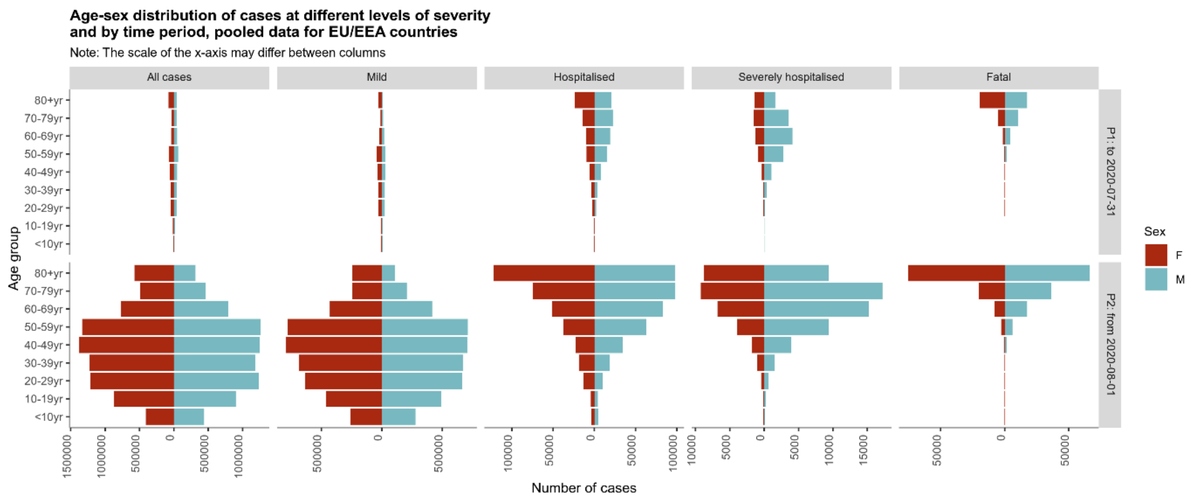
Country where the variant has been detected	Date of first detection	Places of emergence	Number of cases by late December 2022 to early January 2023
USA	22nd October 2022	New York	40%
France	2nd January 2023		15 cases
Germany	Early January 2023	Brandenburg	Not disclosed
Canada	4th January 2023	Alberta	1 case
Australia	3rd January 2023	New South Wales	8 cases
India	Early January 2023	Gujarat, Karnataka, and Rajasthan	5 cases
New Zealand	1st week of January 2023		2 cases
Fiji Island	Late 1st week of January 2023	Fiji's border	Not disclosed

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

The ECDC collects 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[17] enabling estimates of age and gender distribution representative of the European population. The ECDC website posted a notice that the 04 November 2021 edition of the COVID-19 surveillance report would be the last and that it would not be updated in that form in the future. Henceforth, surveillance data would be reported in a weekly "Country Overview Report" that provides less age-based information and no gender-based information.

Here we present relevant age- and gender-based data from the final edition of the more comprehensive COVID-19 surveillance report on 04 November 2021, as well as available age-based data from the most recent edition (23 December 2021) of the Country Overview Report. TESSy data on age and sex distributions by severity of symptoms as posted on 04 November 2021 are shown in Figure 4.[18]

Figure 4. 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 04 November 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 43, 2021. 04 November 2021. "2.2 Age-sex pyramids" Accessed 26 March 2022.

US distributions of reported COVID cases and deaths as of 28 December 2022 are stratified by demographics and presented in Table 3 and Table 4.[19] Only cases and deaths with information reported to the CDC were included in these summaries.

Table 3. Distribution of Cases (n=94,447,829) by Age, Sex, Race, and Cross-Tabulated Age and Sex -- United States as of 28 December 2022[a]

Event	Age Group	Age %	Sex	Sex %	Race	Race[b] %	Age Group	Females %	Males %	Other %
Cases	0-4	3.6	Females	53.8	H/L	24.7	0-4	47.9	52.1	<0.1
	5-11	6.5	Males	46.2	AI/AN	0.9	5-11	48.8	51.2	<0.1
	12-15	4.5	Other	<0.1	Asian	4.4	12-15	50.5	49.5	<0.1
	16-17	2.6			Black	12.4	16-17	52.8	47.2	<0.1
	18-29	20.4			NH/PI	0.3	18-29	55.4	44.6	<0.1
	30-39	16.7			White	53.4	30-39	55	45	<0.1
	40-49	14.2			M/O	3.9	40-49	54.8	45.1	<0.1
	50-64	18.5					50-64	53.5	46.5	<0.1
	65-74	7.3					65-74	52.6	47.4	<0.1
	75-84	3.8					75-84	53.8	46.2	<0.1
	85+	1.9					85+	62.9	37.1	<0.1

a. Percentage of missing demographic data varied by types of event and demographic. Race/ethnicity available for 64% of cases, age available for 99% of cases, and sex available for 96.7% of cases.

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 4. Distribution of Deaths (n=937,757) by Age, Sex, Race, and Cross-Tabulated Age and Sex -- United States as of 28 December 2022[a]

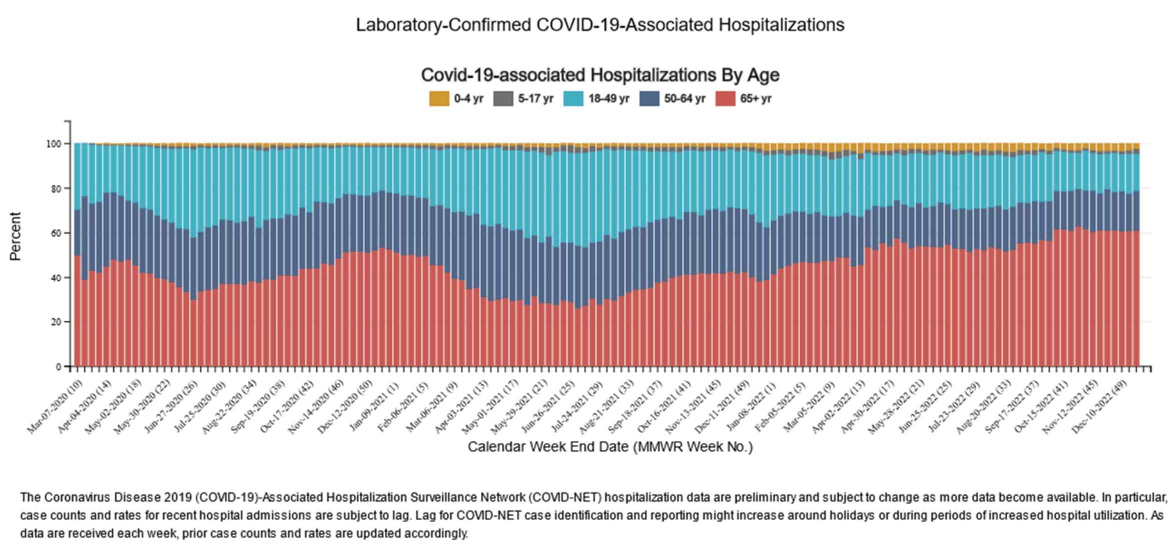
Event	Age Group	Age %	Sex	Sex %	Race[b]	Race %	Age Group	Females %	Males %	Other %
Deaths	0-4	0.1	Females	45	H/L	17.1	0-4	46.4	53.6	<0.1
	5-11	0.1	Males	55	AI/AN	0.9	5-11	43.8	56.2	<0.1
	12-15	0.1	Other	<0.1	Asian	3.2	12-15	51.9	48.1	<0.1
	16-17	<0.1			Black	13.2	16-17	38.3	61.7	<0.1
	18-29	0.7			NH/PI	0.2	18-29	39.6	60.4	<0.1
	30-39	1.8			White	63.2	30-39	39	61	<0.1
	40-49	4.1			M/O	2.2	40-49	37.4	62.6	<0.1
	50-64	17.8					50-64	38	62	<0.1
	65-74	22.4					65-74	40.6	59.4	<0.1
	75-84	26					75-84	44.1	55.9	<0.1
	85+	27					85+	56	44	<0.1

a. Percentage of missing demographic data varied by types of event and demographic. Race/ethnicity available for 83% of deaths, age data available for 99% of deaths, and sex available for 97% of deaths.
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.

The Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) performs population-based surveillance for laboratory-confirmed SARS-CoV-2-associated hospitalizations in the US. Cases are identified by reviewing hospital, laboratory, and admission databases and infection control logs for patients who are hospitalized and have a documented positive SARS-CoV-2 test.[20]

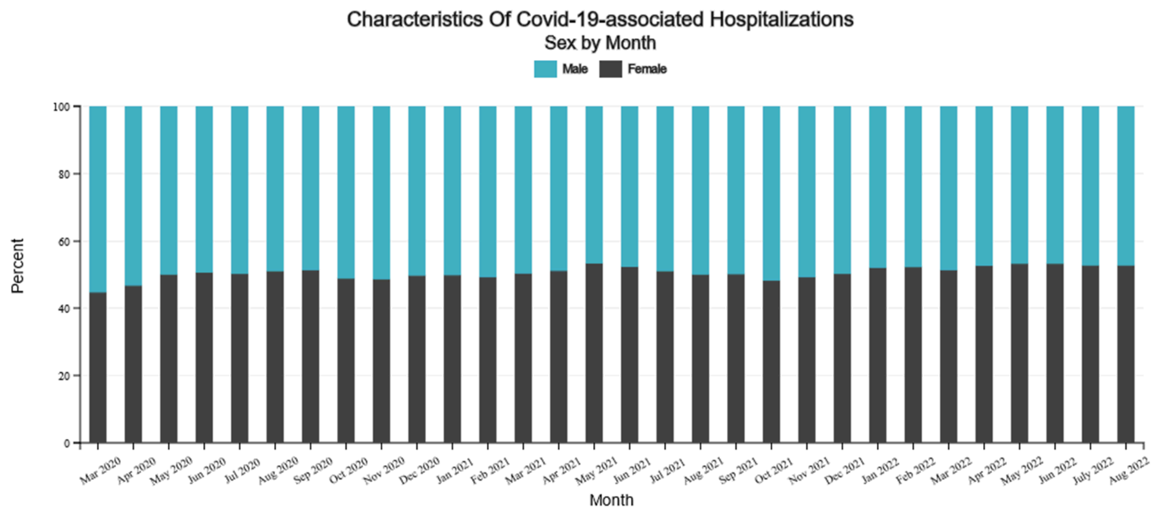
Based on data from COVID-NET, COVID-19 associated US hospitalizations, by age, for the period March 7, 2020, through December 10, 2022, are shown in Figure 5.[21]

Figure 5. COVID-19-Associated US Hospital Admissions by Age, March 2020 - December 2022



Based on data from COVID-NET, COVID-19 associated US hospitalizations, by sex, for the period March 2020, through August 2022, are shown in Figure 6. [21]

Figure 6. COVID-19-Associated US Hospital Admissions by Sex, March 2020 - August 2022



1. The Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) hospitalization data are preliminary and subject to change as more data become available. In particular, case counts and rates for recent hospital admissions are subject to lag. Lag for COVID-NET case identification and reporting might increase around holidays or during periods of increased hospital utilization. As data are received each week, prior case counts and rates are updated accordingly.
2. White, Black, Asian/Pacific Islander and American Indian/Alaska Native all represent non-Hispanic ethnicity groups; Other includes persons in multiple race categories and persons for whom race is unknown.
3. All data presented, including demographics (age, sex, race and ethnicity), interventions and outcomes, underlying medical conditions, signs/symptoms at admission and discharge diagnoses are restricted to sampled and completed cases with non-missing data reported during March 1, 2020 – August 31, 2022. Due to the sampling methodology for adults aged ≥18 years, counts and unweighted percentages are only presented for demographic data. Weighted percentages are presented for intensive care unit admission, mechanical ventilation, in-hospital death, underlying medical conditions, signs/symptoms at admission, and discharge diagnoses. MD did not contribute data between December 2021 and June 2022.

Published studies have provided demographics of patients affected by COVID-19. In a study that analyzed data from 1,164 symptomatic, molecularly confirmed hospitalized (admitted between 5 May 2020 and 19 March 2021) COVID-19 patients from 20 different hospitals across the US, the median age was 59.0 years (intra-quartile range 20 years) and 61% of the patients were male. The racial/ethnic distribution of the patients was 48% white, 22% black, 5% Asian, 31% Hispanic and 65% non-hispanic.[22]

An observational, retrospective study examined patients ≥18 years old with confirmed COVID-19 presenting to the Emergency Departments of 10 hospitals in the United Kingdom, Italy, Spain, and Switzerland, predominantly during the first wave of the pandemic. Those who were not admitted to hospital were a mean age of 51.6 (± 12.8) years old and 51.9% of them were male. Those admitted to hospital were analyzed separately according to whether they survived or not. The mean ages of those admitted were 62.5 (+/- 15.3) years and 62.6% were males for those who survived. For those who did not survive, mean age was 71.3 (+/- 12) years and 70.6% were male.[23]

Another study used data from the Primary Care Sentinel Cohort of the Oxford Royal College of General Practitioners Research and Surveillance Centre database, which is considered to be nationally representative of the English population, to identify COVID-19 cases from 1 March 2020 to 1 April 2021. Overall, the investigators identified 395,680 persons with

COVID-19 among the 7,382,775 persons registered in the database. The mean (sd) age of those infected was 44.56 (21.75) years; 55.6% of them were female; the racial distribution was 65.1% white, 2.8% black, 8.7% Asian, 2.3% other and 21.1% unknown; and 57% of them were from the “most deprived” socio-economic category.[24]

As of January 20, 2022, Omicron had been identified in all EU/EEA countries.[25] The median age of the 155,150 cases reported to TESSy by EU/EEA countries up to that point was 30 (interquartile range 20–33) years; 7% were aged 60 years and above and 50% were male.[26]

A study using data from 17 of 18 regional health agencies in France examined the demographic characteristics of 468 confirmed cases of the Omicron variant from 23 November 2021 to 11 January 2022. The cases were of a median age of 35 years, 55% female, and only 16% had pre-existing conditions (hypertension, obesity, diabetes, chronic respiratory disease, renal insufficiency, cancer, immunosuppression, liver disease, heart disease, neuromuscular condition, pregnancy, or other condition).[26] A study of SARSCoV-2 Omicron variant cases in Denmark used data from the routine Danish surveillance of COVID-19 in which information from several national registries is linked daily. As of 09 December 2021, 785 cases of SARS-CoV-2 Omicron had been registered in Denmark. The median age of the cases was 32 years (range 2 to 95) and 433 (55%) were male.[27]

In one US-based study, the mean age and gender distribution of persons infected with the Omicron variant of the COVID 19 virus was similar to that of persons infected with prior strains; the study, conducted using electronic health records from a large community health system, examined the outcomes of patients admitted to hospital for COVID-19 infection during 3 time periods: March 2020–June 2021 (pre-Delta period), July–November 2021 (Delta period), and December 2021-February 2022 (Omicron period). Patients infected had a mean age 57.7, 58.8 and 61.0 years for the pre-Delta, Delta and Omicron periods, respectively, and were male 51.0%, 53.3% and 50.3 % for the pre-Delta, Delta and Omicron periods, respectively.[28]

A study in South Africa using data from 49 acute care hospitals compared demographic characteristics and outcomes in patients hospitalized for COVID-19 during 4 time periods:

1. June to August 2020 (ancestral COVID-19 variant),

2. November 2020 to January 2021 (Beta variant),

3. May to September 2021 (Delta variant), and

4. (November 15 to December 7, 2021 (Omicron variant). Patients hospitalized during period 4 (Omicron) were younger (median age, 36 years vs 53-59 in the prior 3 periods), more likely female (60.8% vs 46.3–51.8% in prior 3 periods), less likely to have comorbidities (23.3% vs 52.5 -58.4% in prior 3 periods), and less likely to present with an acute respiratory condition (31.6% vs 72.6-91.2% in prior 3 periods).[29]

A similar study in the US used data from a genome sequencing study of SARS-CoV-2 in the Houston Methodist health care system. The authors identified 4468 symptomatic patients with infections caused by Omicron from late November 2021 through January 5, 2022.

Compared with earlier patients infected with either Alpha or Delta variants in the health care system, Omicron patients were significantly younger, more likely to be female, and more likely to be African American. Of note, this study found that the Omicron variant was associated with more vaccine breakthrough cases than previous variants of SARS-CoV-2.[30]

Another similar study described characteristics and outcomes abstracted from the electronic health records of adults aged ≥18 years admitted to one academic hospital with confirmed SARS-CoV-2 infection during periods of Delta (July 15-September 23, 2021) and Omicron predominance (December 21, 2021-January 27, 2022) in Los Angeles, California. The authors reported that the median age of the patients admitted during the period of Omicron predominance was older (median 66 v. 60 years, $p<0.01$) than those admitted during the period of Delta predominance. The proportion of female cases was greater during the Omicron period (48.8% v 44.0%, $p=0.15$) but females were the slight minority compared with males during both the Delta and Omicron periods. There was no difference in terms of race/ethnicity during the two periods.[31]

A CDC study of Omicron transmission within households in 4 US jurisdictions found that age was not related to transmission: Omicron attack rates were high across all ages regardless of vaccination status.[32] A study of COVID-19 reinfections using Italian national data found that, during the period when Omicron was the dominant strain, those over age 60 had a greater risk of severe reinfection (i.e. severe symptoms during a second infection), but the elderly did not have greater risk for overall reinfections.[33] In terms of race/ethnicity, a CDC study of 14 states found that during the Omicron-predominant period, peak hospitalization rates among non-Hispanic African American adults were nearly four times the rate of non-Hispanic White adults and was the highest rate observed among any racial and ethnic group during the pandemic.[34] This same 14-state CDC study found that, compared with the Delta-predominant period, the proportion of unvaccinated hospitalized African American adults increased during the Omicron-predominant period.

An analysis of US data from 2020 showed that 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.[35] Early in the pandemic in the US, approximately 90% of hospitalized cases were over 40 years old, and the majority had been male, although currently there is an approximately equal distribution in sex.[36-40]

African American COVID-19 patients have been reported to have an increased risk of hospitalisation[37,41] and mortality,[42] 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.[43] 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, this was the only racial or ethnic group among whom the percentage of deaths increased during that time.

An earlier CDC report on excess deaths covering 26 January 2020 through 03 October 2020 broke down excess deaths by demographics.[44] By age during that period, the largest increase in deaths compared to average expected deaths occurred among adults aged 25-44 (26.5% increase) while deaths among people <25 years was 2.0% below average during this period.

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).

In a 2021 report, the CDC data on Excess Deaths Associated with COVID-19 reported that deaths in age groups 25-44, 45-64, 65-74, 85-84, and ≥ 85 years exceeded historical numbers from 2015-2019.[45] An increase in deaths can be observed around week 35 that coincided with the wave of Delta variant infections, with the largest number of deaths occurring in the 45-64 age group at 16,362.

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 01 - March 31, 2021 across 14 states (the most recently available data), the CDC's Coronavirus Disease 2019 (COVID-19) - Associated Hospitalization Surveillance Network (COVID-NET) database recorded 204 adolescents aged 12-17 who were hospitalized for likely primarily COVID-19-related reasons.[46] 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.[46]

For the period March 7, 2020 - December 24, 2022, the CDC's COVID-NET database recorded that 6,434 children aged 0-4 had a positive COVID test proximal to hospitalization and 6,239 children aged 5-17 had a positive COVID test proximal to hospitalization.[47]

Another 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.[48] The report broke down incidence by age groups and 2020 sub-periods that are presented in Table 5. 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 5. COVID-19 incidence and rate ratios, by age group among persons aged <25 years across three periods of 2020 in 16 U.S. jurisdictions

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 6 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.[49] The table shows that, among the paediatric population, children aged 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.

Table 6. Demographics of 135,794 US individuals under age 25 tested for COVID-19 by 08 September 2020

	Patients, n (%)		
Characteristic	**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

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 6, 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.[50]

A retrospective study of public health surveillance data in Denver, Colorado identified 9,815 children and adolescents who had COVID-19 from March 1, 2020, through September 30, 2021. The age distribution of those infected was as follows: <1 year 4.9%, 1-4 years 16.3%, 5-10 years 29.6%, 11-13 years 18.4%, and 14-17 years 30.8%. The cases were 50% male and 50% female. The racial / ethnic distribution was Hispanic / Latino 57.3%, non-Hispanic White 29.0%, non-Hispanic Black 7.1%, and non-Hispanic other 6.5% from a base population that was Hispanic / Latino 46.3%, non-Hispanic White 36.9%, non-Hispanic Black 12.0%, and non-Hispanic other 4.9%.[51]

Risk Factors

Human-to-human transmission of SARS-CoV-2 occurs primarily through respiratory droplets and direct contact.[52] Thus the risk of initial infection increases through spending time in close physical proximity to others, especially in indoor spaces with poor ventilation.[53] 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.[53,54] Among children, the primary source of infection is an infected adult living in the same household[55], but age is not associated with risk of initial infection among people aged 5 years and older based on current data from the CDC.[56,57]

According to the CDC, some ethnic minority groups have a higher risk of infection (Table 7).[57] Male sex is also a significant risk factor for severe disease and mortality due to COVID-19.[58] In addition, there is evidence that high-risk human leukocyte antigen haplotypes, higher expression of angiotensin-converting enzyme polymorphisms, and several genes of cellular proteases increase the risk of susceptibility and severity of COVID-19.[59,60] Lastly, recent narrative reviews and meta-analyses indicate that Blood type O is associated with lower rates of SARS-CoV-2 infection; whereas type A is frequently described as a risk factor and is most often associated with COVID-19 severity and mortality.[61,62]

Table 7. Risk for COVID-19 Infection, Hospitalization, and Death in US by Age Group and by Race/Ethnicity as of 28 December 2022

		Rate ratios[a]	
Age Group (years)	**Cases[b]**	**Hospitalization[c]**	**Death[d]**
0-4	0.5	0.6	0.2
5-17	0.7	0.2	0.1
18-29[e]	Ref	Ref	Ref
30-39	1	1.5	3.5
40-49	0.9	1.9	10
50-64	0.8	3.1	25
65-74	0.6	4.8	60
75-84	0.6	8.6	140
85+	0.7	15	350
Race/Ethnicity			
	Cases[f]	**Hospitalization[g]**	**Death[h]**
Non-Hispanic White	Ref	Ref	Ref
American Indian or Alaska Native, non-Hispanic	1.5	2.5	2.1
Asian, non-Hispanic	0.8	0.7	0.8
Black or African American, non-Hispanic	1.1	2.1	1.6
Hispanic or Latino	1.5	1.9	1.7

a. Rates for age groups 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. Rates for race/ethnicity groups are rounded to the nearest tenth.
b. Includes all cases reported by state and territorial jurisdictions (through 06 December 2022, accessed on 13 December 2022). The denominators used to calculate rates were based on the 2019 Vintage population (https://www.census.gov/newsroom/press-releases/2019/popest-nation html).
c. Includes all hospitalizations reported through COVID-NET (from 01 March 2020 through 04 December 2022, accessed on 13 December 2022). Rates were standardized to the 2000 US standard COVID-NET catchment population.
d. Includes all deaths in National Center for Health Statistics (NCHS) provisional death counts (through 03 December 2022, accessed on 13 December 2022. The denominators used to calculate rates were based on the 2019 Vintage population.
e. 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.
f. Case level surveillance data from state, local and territorial public health jurisdictions (data through 7 December 2022). Numbers are ratios of age-adjusted rates standardized to the 2019 U.S. intercensal population estimate. Calculations use only the 65% of case reports that have race and ethnicity; this can result in inaccurate estimates of the relative risk among groups.
g. Includes all hospitalizations reported through COVID-NET (1 March 2020 through 3 December 2022). Numbers are ratios of age-adjusted rates standardized to the 2020 US standard COVID-NET catchment population.
h. Includes all deaths in National Center for Health Statistics Provisional Death Counts (data through December 3, 2022). Numbers are ratios of age-adjusted rates standardized to the 2019 U.S. intercensal population estimate.

Risk for severe or fatal COVID-19 disease has been shown to increase with older age, male sex, or ethnic minority status.[56,57,59,63-69] Among adults, these risks increase for every 10-year age group above age 39.[56,70]

Table 7 also gives estimated rate ratios for COVID-19 hospitalisation and death by race/ethnicity relative to white, non-Hispanic persons in the US. Based on regularly updated data from the CDC, the highest risk of hospitalization and death occurred in those who were American Indian or Alaska native persons (RR = 2.5 for hospitalization, RR =2.1 for death), when compared to those who were non-Hispanic white.

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.[57]

Children aged 5-17 typically experience a milder disease course and have lower risk of hospitalization or death.[57,66,70] Further, among a cohort of children hospitalised with COVID-19 in the United States from March 2020 to May 2021, infants and children 6 months - 4 years of age had a similar risk of severe disease as children ages 12 - 17 years.[71]

Risk of severe or fatal COVID-19 disease is also 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.[45,52,64,68,72,73] The CDC has also recognised other socio-demographic groups who may need to take extra precautions against COVID-19 due to increased risk for severe illness: pregnant women; breastfeeding mothers; people with disabilities or those who are clinically frail; people with developmental, behavioural or substance abuse disorders; and newly resettled refugee populations.[74]

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), hypertension, cardiovascular disease, diabetes, cancer, liver disease, neurological diseases (e.g., stroke or dementia), chronic kidney disease, anaemia, sickle cell disease, immunosuppression, HIV, mycotic infection, vitamin D deficiency higher scores on the WHO Clinical Progression Scale and Charlson Comorbidity Index [63,64,68,70,75-89]

Several studies have examined risk factors for infection with the Omicron variant and outcomes of the disease.

A study of COVID-19 reinfections using Italian national data from August 2021 through March 2022 (periods of Delta and Omicron predominance) found that, for all variants, the strongest risk factor for reinfection, but not severe reinfection, was being unvaccinated (close to 3-fold) compared to those who were vaccinated for ≤120 days; the risk of reinfection was highest during Omicron regardless of vaccination status. Unvaccinated was defined as never received a dose or <14 days from 1st dose. Vaccinated was defined as at least 1 dose and ≥ 14 days from last dose. Reinfections were defined as infection ≥90 days after 1st infection.[33] Having been vaccinated more than 120 days prior was also correlated with a greater risk of reinfection, presumably due to vaccine efficacy waning over time. Strikingly, reinfection with Omicron was 18 times the risk of reinfection with Delta regardless of vaccination status; however, severe reinfections with Omicron were only 0.37 times the risk of reinfection with Delta.

The WHO report on rapid risk assessment reported several key factors which may result in a rapid spread of omicron variant XBB.1.5 compared to its parent lineage XBB.1.

According to the analysis of a large international COVID-19 cohort of 600,000 hospitalised patients with COVID-19, age [adjusted hazard ratio per 10 years 1.49 (95% CI 1.48, 1.49)] and male sex [1.23 (1.21, 1.24)] were associated with a higher risk of death.[90]

Current and former smokers are at higher risk of dying from COVID-19. A meta-analysis confirmed the association between current smoking (odds ratio [OR] 1.26, 95% confidence interval [CI]: 1.01-1.58) and former smoking (OR 1.76, 95% CI: 1.53-2.03) with COVID-19 mortality.[91]

There is currently no evidence that infection severity of XBB.1.5 is different than that of previously circulating Omicron sub-lineages. However, an increase in cases caused by increased transmissibility or immune escape would be expected to lead to an increase in the number of severe cases. In hamsters, the virological characteristics in vivo and intrinsic pathogenicity of XBB is comparable to the BA.2.75 sub-lineage, and lower than Delta VOC based on body weight, pulmonary function, efficacy of viral spread in the respiratory tissues and histopathological assessments reported in a preprint study . The results suggest that XBB is less pathogenic than Delta and comparable with BA.2.75. No in vitro or in vivo studies have yet been reported for the XBB.1.5 sub-lineage specifically.[92]

Table 8 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.[76]

Table 8. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death

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 8. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death

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. Index of Multiple Deprivation (derived from the patient's postcode)

b. Classification by HbA1c is based on the most recent measurement within 15 months of baseline.

c. eGFR is measured in ml min−1 per 1.73 m^2 and derived from the most recent serum creatinine measurement. 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."

A recent prospective observational study sought to better understand the association between characteristics of adult patients hospitalized with COVID-19 in the US and the risk of clinical outcomes and post-acute clinical sequalae of COVID-19 (PASC). [22] A total of 1,164 patients symptomatic patients admitted to 20 hospitals (affiliated with 15 academic institutions) across the US were enrolled. Admission-specific data elements were acquired via review of electronic medical records at 5 separate time-points over a 28-day period. The patients' disease severity was assessed at each time-point using a 7-point ordinal scale (ranging from not hospitalized/no limitations to death) based on World Health Organization and US National Institute of Allergy and Infectious Disease severity scales. Data lock on the survey data was performed on April 7, 2022. The median age was 59 years (interquartile range 20); 711 (61%) were men; the overall mortality was 14%, and 228 (20%) of the patients required invasive mechanical ventilation. The authors report that risk factors associated with prolonged hospitalization or death by day 28 included age ≥65 years, Hispanic ethnicity, elevated baseline creatinine or troponin, baseline lymphopenia, presence of infiltrate by chest imaging, and high SARS-CoV2 viral load. Survivors were prospectively surveyed for 1 year after discharge through quarterly surveys. Of these 589 completed at least one survey at follow-up. Three hundred five 52% of those completing at least one survey had at least one symptom consistent with PASC, most commonly dyspnoea. Female sex was the only associated risk factor for PASC).[22]

Another recent study by Tsai et al was conducted with the aim to estimate the global risk and risk factors associated with acute respiratory distress syndrome among patients with COVID-19. The authors performed a systematic review, meta-analysis and meta-regression of published studies from of patients in hospitals or nursing homes with acute respiratory distress syndrome (ARDS) after COVID-19. Study inclusion criteria were: (1) the study provided primary data on the prevalence of ARDS using validated assessment tools or coded medical report data within a population-based study after COVID-19 occurred; (2) patients were diagnosed with COVID-19; and (3) the studies were observational, such as cohort and cross-sectional studies, and were published from 2019 to 2022. A total of 12 studies, conducted in 7 countries (including the US, China, Korea, India, Germany, Poland and Greece) were included. Six studies were retrospective three were cross-sectional, two were cohort studies, and one was a prospective study. All 12 studies were conducted with hospitalized patients. A total of 148,080 patients (50.8% male) were studied. The prevalence of ARDS among the studies ranged from 3.6% to 76.4%; the overall pooled risk was 23% (95% CI 14.3–34.7%) with significant heterogeneity within the 12 studies. Based on the meta-analysis results, significant heterogeneity was identified among the studies for the risk of ARDS. Therefore, a meta-regression analysis was conducted to identify factors affecting heterogeneity through the subgroups. Meta-regression revealed that statistically significant risk factors for ARDS included: age ≥41 to 64 years, fever, multi-lobe involvement on chest X-ray, lymphopenia, mechanical ventilation with oxygen therapy, European region, and study sample size less than or equal to 500 patients.[93]

The presence of one or more underlying medical conditions also increases risk of severe or fatal disease among children aged 5-17. [94-96] In particular, childhood obesity has been consistently associated with two to three times the risk of severe disease or hospitalization[97,98] and among hospitalized children with COVID-19 diabetes has been shown to increase the risk of death two-fold compared with those without diabetes.[99] In addition, children and adolescents with obesity, hypertension, immunodeficiencies, malignancies, chronic respiratory diseases (cystic fibrosis, severe asthma etc.), and other chronic diseases are more susceptible to developing severe disease.[100] 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.[66,95]

The US Centers for Disease Control (CDC) investigated the effectiveness of Omicron household transmission prevention strategies during November 2021 to February 2022. Persons with confirmed Omicron infection and their household contacts were interviewed. Omicron transmission occurred in 124 (67.8%) of 183 households. Among 431 household contacts of index Omicron cases, 227 were classified as having a case of COVID-19 (attack rate [AR] = 52.7%). The AR was lower among household contacts of index patients who isolated compared with those of index patients who did not isolate (41.2% vs 67.5%, respectively; $p < 0.01$). Similarly, the AR was lower among household contacts of index patients who ever wore a mask at home during potentially infectious period (88 of 223) compared with those of index patients who never wore a mask at home (39.5%, vs 68.9%

respectively; $p<0.01$).[32] The study also found that age was not a risk factor for Omicron transmission, as attack rates were high across all ages.[32]

In addition to risks of overall reinfections, the Italian study also looked at severe reinfections, that is, second infections in which the symptoms are severe. They found that being over 60 years old, and having had a severe first infection, were risk factors for a severe reinfection. We cannot exclude the possibility that some reinfections in the unvaccinated group are in individuals within 14 days of their 1st dose, known to be a susceptible period.

A CDC study of adults in 14 states found some evidence that race/ethnicity may have been a risk factor for COVID-19-related hospitalization during the Omicron-predominant period. The authors reported that peak hospitalization for any diagnosis in patients who tested positive during that time among non-Hispanic African American adults were nearly four times the rate of non-Hispanic White adults and was the highest rate observed among any racial and ethnic group during the pandemic.[34] In this study, unvaccinated was defined as receiving no doses of vaccine. This same 14-state CDC study found that, compared with the Delta-predominant period, the proportion of unvaccinated hospitalized African American adults increased during the Omicron-predominant period.

US FDA approved or authorized treatment options

Through January 2023, other COVID-19 vaccines were authorized and recommended for use in the United States including vaccines from Moderna (NCT04470427), and Johnson & Johnson/Janssen (NCT04505722). Others may subsequently be approved. The Pfizer-BioNTech COVID-19 vaccine, Comirnaty, received FDA approval on 23 August 2021 for individuals 16 years of age and older[101] and received an emergency use authorization (EUA) in children 5 through 11 years of age on 29 October 2021.[102] Novavax Adjuvanted COVID-19 Vaccine received an EUA on 13 July 2022 for those 18 years of age and older.[103]

EUA authority was also used to make treatments available in patients with COVID-19 ahead of formal approval. These products include direct treatment for COVID-19 infections and for other medical conditions in infected persons (Table 9).[103]

Table 9. Drugs or Non-Vaccine Biologics with Emergency Use Authorization or Full Approval from the FDA

Date of Issuance	Drug or Non-Vaccine Biologic	Authorized Use
4/30/2020	Fresenius Medical, multiFiltrate PRO System and multiBic/multiPlus Solutions [also listed under Medical Device EUAs].	To provide continuous renal replacement therapy (CRRT) to treat patients in an acute care environment during the COVID-19 pandemic.
5/1/2020	Remdesivir for Certain Hospitalized COVID-19 Patients (EUA reissued August 28, 2020, October 1, 2020, and October 22, 2020)	For emergency use by licensed healthcare providers for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. On October 22, 2020, FDA approved remdesivir (Veklury) for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization.
5/8/2020	Fresenius Kabi Propoven 2%	To maintain sedation via continuous infusion in patients older than age 16 with suspected or confirmed COVID-19 who require mechanical ventilation in an ICU setting.
8/13/2020	REGIOCIT replacement solution that contains citrate for regional citrate anticoagulation (RCA) of the extracorporeal circuit	To be used as a replacement solution only in adult patients treated with continuous renal replacement therapy (CRRT), and for whom regional citrate anticoagulation is appropriate, in a critical care setting
8/23/2020	COVID-19 convalescent plasma (EUA reissued February 23, 2021, March 9, 2021, and December 28, 2021)	COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.
11/19/2020	Baricitinib (Olumiant) (Revised December 20, 2021)	For emergency use by healthcare providers for the treatment COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
11/21/2020	REGEN-COV (Casirivimab and Imdevimab) (EUA reissued February 3, 2021, February 25, 2021, June 3, 2021, July 30, 2021, September 9, 2021, and November 17, 2021)	Casirivimab and imdevimab to be administered together for the treatment of mild to moderate COVID-19 in adults and paediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalisation or death.
2/9/2021	Bamlanivimab and Etesevimab (EUA reissued February 25, 2021, August 27, 2021, September 16, 2021, December 3, 2021, and December 22, 2021)	Bamlanivimab and etesevimab administered together for the treatment of mild-to-moderate COVID-19 in adults and paediatric patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalisation or death.
3/12/2021	Propofol-Lipuro 1%	To maintain sedation via continuous infusion in patients greater than age 16 with suspected or confirmed COVID-19 who require mechanical ventilation in an ICU setting.

Table 9. Drugs or Non-Vaccine Biologics with Emergency Use Authorization or Full Approval from the FDA

Date of Issuance	Drug or Non-Vaccine Biologic	Authorized Use
5/26/2021	Sotrovimab (EUA reissued October 8, 2021, and December 16, 2021)	For the treatment of mild-to-moderate COVID-19 in adults and paediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalisation or death.
6/24/2021	Actemra (Tocilizumab)	For the treatment of COVID-19 in hospitalized adults and paediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
12/8/2021	Evusheld (tixagevimab co-packaged with cilgavimab) (EUA reissued December 20, 2021)	For emergency use as pre-exposure prophylaxis for prevention of COVID-19 in adults and paediatric individuals (12 years of age and older weighing at least 40 kg): - Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination or - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).
12/22/2021	Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use)	Paxlovid is authorized for the treatment of mild-to-moderate COVID-19 in adults and paediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalisation or death.
12/23/2021	Molnupiravir	Molnupiravir is authorized for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19, including hospitalisation or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.
2/11/2022	Bebtelovimab	Bebtelovimab is authorized for the treatment of mild-to-moderate COVID-19 in adults and paediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

Table 9. Drugs or Non-Vaccine Biologics with Emergency Use Authorization or Full Approval from the FDA

Date of Issuance	Drug or Non-Vaccine Biologic	Authorized Use
11/08/2022	Kineret	Kineret (anakinra) is authorized for the treatment of COVID-19 in hospitalized adults with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).
4/4/2023	Gohibic	Gohibic[2] is authorized for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO).

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

Symptoms of COVID-19

Symptoms of COVID-19 infection can range from very mild (or no symptoms) to severe or fatal.[104-107] The most common symptoms for symptomatic infected persons are fever, dry cough, and fatigue; upper respiratory tract symptoms can include pharyngalgia, headaches, and myalgia.[52] Current data indicate that about 80% of COVID-19 patients are asymptomatic or have mild-to-moderate symptoms, while about 15% develop more severe disease requiring hospitalization and about 5% require ventilation support.[52] In addition, 10–20% of COVID-19-infected persons experience persistent or new symptoms for periods of weeks to years.[52]

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.[107] The most common symptoms of COVID-19 are fever, cough, and shortness of breath for both children and adults (Table 10).[108,109] However, it has been noted that in older people, COVID-19 clinical presentation is extremely heterogeneous and atypical signs and symptoms such as hyporexia / apyrexia, confusion, delirium, and pre-syncope / syncope are more common than in middle-aged and younger persons.[110] A recent meta-analysis has estimated that 46.7% of infections in children are asymptomatic, while a recent systematic review that examined 1,140 cases of COVID-19 in children from 23 published studies found that 11% of cases were asymptomatic. Among symptoms, fever was reported in 48%, cough 37%, any nasopharyngeal symptom 22%.[111]

[2] https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

In a more recent meta-analysis of 32 studies that provided information about COVID-19 infection in paediatric patients the proportions with specific symptoms were as follows: fever 33%, cough 25%, rhinorrhoea 13%, fatigue 9%, dyspnoea 9%, diarrhoea 6%, headache 9%, sore throat 7% and vomiting 7%.[112]

Table 10. 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 diarrhoea. 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.

Among the first 43 cases of Omicron identified in the US between December 1-8, 2021, 93% were symptomatic. The initial signs and symptoms reported were cough (89%), fatigue (65%), congestion or runny nose (59%), fever (38%), nausea or vomiting (22%), shortness of breath or difficulty breathing (16%), diarrhoea (11%), and loss of taste or smell (8%).[113] In a recent study of 338 cases in the Omicron period and 441 cases in the Delta comparator period, there was a decreased prevalence of self-reported loss of taste during the Omicron period (26.9% v. 57.4%, p<0.001).[114] Although the majority of the 486 earliest cases of Omicron in France were symptomatic (89%), cases only reported mild symptoms that lasted a median of 4 days (IQR 2-7).[26]

The most common symptoms in hospitalized 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%).[115-118]

COVID-19 patients also commonly experience gustatory disorders (44%) and olfactory disorders (53%).[119] Patients hospitalized in South Africa during the Omicron wave were less likely to present with an acute respiratory condition than in previous waves of the pandemic (31.6% v. 72.6-91.2%, p<0.001).[29] Of note, among the 971 patients admitted during the Omicron wave 24.2% were vaccinated, 66.4% were unvaccinated, and vaccination status was unknown for 9.4%.[29] 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.[116] Approximately 17% to 40% of those hospitalised with COVID-19 experience severe symptoms necessitating intensive care[36,41,115] 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.[50,115] More than 75% of patients hospitalised with COVID-19 require supplemental oxygen.[120]

In their review of COVID-19 infection in children before and after Delta and Omicron variants, Khemiri et al report that the signs and symptoms of infection observed in paediatric patients with Delta and Omicron variants are the same as those observed in children infected before the emergence of these variants.[121]

Symptoms specific to patient with XBB.1.5:

According to American Medical Association (AMA), COVID symptoms have become less severe over time and as a result of the emergence of Omicron and its sub-variants.[12] As per WHO rapid risk assessment report for XBB.1.5 released on 11 Jan 2023, XBB1.5. does not carry any mutation known to be associated with potential change in severity. However, the confidence in the assessment was low.[122] According to an early 2023 study, there were no differences in clinical severity of XBB* and its descendent lineages,[123] as compared to other Omicron lineages and reported mild disease in a small cohort of people infected with XBB.1.5 who all recovered at home with minimal treatment (n=6). Common symptoms included cold and rhinorrhoea (100%), sore throat (50%), fever (66.67%), and cough (33.33%). The symptom profile of this small cohort is consistent with reports that XBB.1.5 produces largely mild cold and flu-like symptoms, with sore throat appearing to be more common, and fewer instances of hyposmia, anosmia, and severe respiratory symptoms, such as shortness of breath.[124,125] According to a Q&A blog from AMA[12], symptoms with XBB.1.5 appear to be similar to the earlier Omicron subvariants. Those can range from typical cold symptoms such as cough and congestion to shortness of breath and low oxygen levels that require emergency medical attention. But as XBB.1.5 continues to spread, the signs and symptoms of COVID-19 may seem different than what was seen earlier in the pandemic with Alpha or Delta variants. Symptoms such as the temporary loss of taste and smell can still happen in some instances, but it has become less common with the Omicron variant and subvariants.

Other symptoms may include fever, chills, fatigue, muscle or body aches, sore throat, nausea or vomiting and diarrhoea. Symptoms can last between five to seven days but vary from person to person.

Preliminary findings from samples sequenced in New York City likewise do not suggest more severe disease among patients infected with XBB.1.5 compared with patients infected with BQ.1.[126]

Sub variants of Omicron, including XBB.1.5, might be less likely to result in severe disease because of two reasons: (1) they tend to remain in the upper respiratory tract thereby reducing the occurrence of lower respiratory tract disease[127] or (2) because populations have some level of immunity from vaccines or prior infection.[12] There are limited data about vaccine effectiveness for XBB.1.5 against symptomatic and severe disease, but available evidence shows that vaccines remain effective against symptomatic disease in people infected with omicron BA.5 and XBB/XBB.1.5 - related sublineages, with protection waning over time.[128]

Many children who develop COVID-19 have no symptoms or experience mild symptoms such as low-grade fever, fatigue, and cough.[129] Compared to adults, COVID infection is much less likely to lead to severe disease or mortality.[130] However, a severe inflammatory condition called multisystem inflammatory syndrome in children (MIS-C) can present 2-6 weeks after infection in a small subset of children.[131,132] MISC-C is characterized by symptoms of inflammation and fever, with impacts across the body including gastrointestinal, respiratory, and neurological systems and, requires a higher rate of critical care support.[133] There are no data currently available on the prevalence of MIS-C following XBB.1.5 infection nor on clinical outcomes,[134] but studies comparing MIS-C diagnoses have found decreasing relative incidences of MIS-C with each wave[134] until Omicron when MIS-C incidence may be increasing.[135,136]

On the basis of early indicators, the WHO noted that there is no evidence of increased disease severity resulting from XBB.1.5 in a risk assessment released in February 2023, labelling it a variant of “interest” but not “concern”.[137] No known mutations associated with potential changes in severity, like those present in Delta,[138,139] were found in the sequencing of XBB.1.5. However, XBB.1.5 remains a variant of interest due to genetic characteristics that increase risk of transmission and mutations that allow it to evade antibodies,[140] which could increase global case counts. More information is needed to make a definitive determination on disease severity and risks to public health of XBB.1.5.

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.[141,142] The average time from exposure to diagnosis was 3.7 days among 107 close contacts of Omicron-positive case patients, with 70% being diagnosed by 5 days, and 99.1% being diagnosed by 10 days.[143] 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-. Data on rates of re-infection are limited but variants may lead to increased risk of re-infection in the future. [111,141,144]

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 entire US by the CDC between 01 August 2020 and 02 January 2023, there were 5,797,528 new hospital admissions for patients who tested positive for COVID-19 in the US.[145] For the 50th week of 2022, 7.6 per 100 000 population (country range: 1.3 - 19.5) were hospitalised due to COVID-19 in 14 countries of the EU/EEA with available data.[146] As of 24 March 2022, 0.1-1.5% of children who tested positive for COVID-19 have been hospitalized (for any diagnosis) based on data reported from 25 states and New York City reporting, and 0.00%-0.01% of children with COVID-19 have died based on data reported from 46 states, New York City, Puerto Rico and Guam.

Between 01 August 2020 and 02 January 2023, the CDC reports 175,603 total hospital admissions for patients with confirmed COVID-19 in the US for those 0-17 years of age.[145]

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.[141] In 9 countries of the EU/EEA with available data, 0.5 per 100 000 population (country range: 0.1-1.3) were in the ICU due to COVID-19 during Week 49 2022.[146] 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.[105] A study of 82 cases in three paediatric hospitals noted that older children and those with higher body mass index or multiple comorbidities were more likely to receive respiratory support.[147]

A large number of patient characteristics (demographic/personal, comorbid conditions, complications of COVID) have been identified as being risk factors of severe COVID, or death from COVID (Table 11).

Table 11. Factors associated with severe disease in those with COVID-19

Demographic Characteristics	Comorbid Conditions	Complications of COVID-19
Male gender[22,58,68,69,76,148] Older age[22,66,68,76,95,148] Ethnic minorities [22,68,70,76,95] Lower socioeconomic status [68,76] Obesity [45,52,66,68,76-78,81,82,95] Smoking[68,72,73,84] Blood group type A[61,62]	Disability/clinical frailty/worse scores on health/comorbidity scales [68,95,149] Cardiovascular disease[52,68,85,148,150] Hypertension[52,68,79-81,84,148,150] Dyslipidemia[81,85] Chronic lung diseases / asthma[22,68,84,85,148,150] Diabetes/higher hemoglobin a1c level[22,52,68,81,84,85,148,150] Cancer[76,84,95,150] Liver disease[76,83,84,95,150] Neurological diseases (e.g., stroke or dementia)[66,68,76,85,95,150] Chronic kidney disease or failure/ elevated baseline creatinine[22,52,66,68,76,85,95,150] Autoimmune disease [68,76,85,150] Immunosuppression/immune compromised[68,76,89,95] Organ transplant[76,84,95] Mycotic infection[150,151] HIV[95] Sickle cell disease[95] Vitamin D deficiency[77,88] Certain genetic polymorphisms[60,152]	Cardiac injury/elevated troponin[22,66,148,150] Arrhythmia[153] Shock[150] Pulmonary embolism[75] Respiratory failure/hypoxia [66,150] GI bleeding[150] Anemia[150] Disseminated intravascular coagulation[150] Rhabdomyolysis[150] Bacterial infection/sepsis[150] Higher neutrophil-to-lymphocyte ratio[154] Electrolyte disturbance[150] Elevated glycated hemoglobin [155] Neutrophilia[66,154] Lymphopenia [22,66,84] Thrombocytopenia [22,66,150,154] High circulating histone levels [156] Lower serum iron or total iron banding capacity[157] Higher serum ferritin levels[157]

Table 11. Factors associated with severe disease in those with COVID-19

Demographic Characteristics	Comorbid Conditions	Complications of COVID-19
		Presence of infiltrate by chest imaging[22,86] High SARS-CoV2 viral load[22]

<u>Risk Factors for Severe Disease and Poor Outcomes Associated with COVID-19 Variants</u>

Recent studies have been published to identify risk factors for hospitalization with variants and according to vaccination status. One such study was conducted by the US CDC using data from COVID-NET, which conducts population-based surveillance for laboratory-confirmed COVID-19 associated hospitalizations in 99 counties across 14 states. The authors examined COVID-19 associated hospitalization rates among adults aged ≥18 years during B.1.617.2 (Delta; July 1 - December 18, 2021; 4,852 cases) and Omicron (December 19, 2021 - January 31, 2022; 829 cases) variant predominance, overall and by race/ethnicity and vaccination status. Vaccination status was identified using state immunization systems data and included the following statuses: unvaccinated, receipt of a primary series only, or receipt of a primary series plus a booster or additional dose. Hospitalization rates during peak Omicron circulation (January 2022) among unvaccinated adults remained 12 times the rates among vaccinated adults who received booster or additional doses (528.2 v. 45.0 per 100,000) and four times the rates among adults who received a primary series, but no booster or additional dose (528.2 v. 133.5 per 100,000). The rate among adults who received a primary series, but no booster or additional dose, was three times the rate among adults who received a booster or additional dose (133.5 v. 45.0 per 100,000).

During the Omicron-predominant period, peak hospitalization rates among non- Hispanic Black (Black) adults were nearly four times the rate of non-Hispanic White (White) adults and was the highest rate observed among any racial and ethnic group during the pandemic.[34]

A study by the Los Angeles County (LAC) Department of Public Health of LAC residents aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection during November 7, 2021, to January 8, 2022, found that unvaccinated persons were more likely to be hospitalized, admitted to an ICU, require intubation for mechanical ventilation, or to die compared with persons who were fully vaccinated with a booster and those fully vaccinated without a booster. Sequencing data were available for 1-18% of specimens during the Omicron period. During the period of Omicron predominance (week ending January 8, 2022), 2.8% of unvaccinated people, 1.0% of fully vaccinated without booster, and 0.7% of fully vaccinated with booster were hospitalized. Unvaccinated persons had infection and hospitalization rates 3.6 and 23.0 times, respectively, those of fully vaccinated persons with a booster and 2.0 and 5.3 times, respectively, higher than those of fully vaccinated persons without a booster.[158]

A second study by the Los Angeles County (LAC) Department of Public Health was done by a cross-sectional analysis of LAC residents aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection during November 7, 2021, to January 8, 2022. Vaccination status was identified using a matching algorithm that links cases to immunization records. Of 422,966 reported SARS-CoV-2 infections in LAC residents aged ≥18 years, 33.6% (n=141,928) were in unvaccinated persons, 13.3% (n=56,185) were in fully vaccinated persons with a booster (considered fully vaccinated with a booster ≥14 days after booster) and 53.2% (n=224,853) were in fully vaccinated persons without a booster (≥14 days after primary series). Hospital admissions for any reason ≤14 days after 1st lab-confirmed positive test were identified. Unvaccinated persons were more likely to be hospitalized, admitted to an ICU, require intubation for mechanical ventilation, or to die compared with persons who were fully vaccinated with a booster and those fully vaccinated without a booster. Sequencing data were available for 1-18% of specimens during the Omicron period. During the period of Omicron predominance (week ending January 8, 2022), 2.8% of unvaccinated people, 1.0% of fully vaccinated without booster, and 0.7% of fully vaccinated with booster were hospitalized. Unvaccinated persons had infection and hospitalization rates 3.6 and 23.0 times, respectively, those of fully vaccinated persons with a booster and 2.0 and 5.3 times, respectively, higher than those of fully vaccinated persons without a booster. [158]

Several international studies have examined the risk of serious disease or death associated with variants of the COVID virus. Chen at al conducted a multicenter observational study during the 2022 Omicron wave in Shanghai, China to examine the prognosis of infection with the Omicron variant among hospitalized patients who were "fragile" or who had "high-risk" comorbidities. Enrolled subjects were adults with confirmed SARS-CoV-2 infection by real-time PCR between 20 March and 10 May 2022. The primary outcome was progression to severe or critical disease consistent with WHO guidelines (Severe disease: one or more of oxygen saturation <93% on room air, signs of pneumonia, and signs of severe respiratory distress; critical disease: acute respiratory distress syndrome, sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies). The study population consisted of 847 patients, of whom 30.3% were age >70 years, 55.8% were not fully vaccinated, and 65.4% had at least one comorbidity (the five most common being 34% heart conditions, 18.5% metabolic disease, 18.4% chronic kidney disease [CKD] stage 4–5, 17.1% isolated hypertension, and 12.5% cancer. A history of being bed-ridden long term was noted in 18.7%. The overall rate for severe and critical cases was 11%. Multivariate analysis showed that comorbidities of CKD stage 4–5, cancer, and long-term bedridden history were risk factors for progression to severe or critical disease, whereas female sex, and fully/booster vaccinated were protective against progression to severe or critical disease.[150]

A study conducted in South Africa aimed to assess the clinical severity of COVID-19 in patients admitted to hospital with laboratory-confirmed SARS-CoV-2 infection during the Omicron, Asp614Gly mutation, Beta variant, and Delta variant waves using data from an active surveillance program established specifically for COVID-19.[159] Included patients had COVID-19 symptoms, were admitted for isolation, acquired nosocomial COVID-19 infection, or tested positive incidentally when admitted for other reasons from March 5, 2020, to Jan 22, 2022. Severe COVID-19 disease was defined as one or more of development of acute respiratory distress syndrome, receipt of oxygen or invasive mechanical ventilation, or treatment in high-care or intensive-care units. In patients with known clinical outcomes, 52.3% in the Asp614Gly wave, 63.4% in the Beta wave, and 63.0% in the Delta wave met the criteria for severe disease, compared with 33.6% in the Omicron wave (p<0·0001). The proportion of patients requiring supplemental oxygen and the median length of hospital stay was also lower in the Omicron wave than in the other three waves (p<0·0001 for each comparison). The in-hospital case-fatality ratio during the Omicron wave was 10.7%, compared with 21.5% during the Asp614Gly wave, 28·.8% during the Beta wave, and 26.4% during the Delta wave (p<0·0001). On multivariable analysis, compared with those admitted to hospital in the Omicron wave, patients were more likely to have severe disease if they were admitted to hospital in the other 3 waves. Other factors associated with severe disease in this patient population were older age, being male, being Indian (compared with being White), presence of a comorbidity, and the province of hospital admission.[159]

With respect to the paediatric population and variant disease, in the South African study mentioned above[159] children and adolescents (<20 years) constituted 14.3% of total hospital admissions in the Omicron wave, compared with 3.3% in the Asp614Gly wave, 3.0% in the Beta wave, and 5.5% in the Delta wave. In children <5 years, the proportion of laboratory-confirmed cases admitted during the Omicron wave was higher than in the other 3 waves (25.4% in Omicron vs 12.9%, 15.1% and 14.7% in the Asp614Gly, Beta, and Delta waves, respectively). In children and adolescents 5-19 years, the proportion of laboratory-confirmed cases admitted during the Omicron wave was also higher than in the other 3 waves (5.7% in Omicron vs 3.7%, 2.7% and 2.3% in the Asp614Gly, Beta, and Delta waves, respectively). However, the proportion of children and adolescents admitted to hospital who received supplemental oxygen, were treated in intensive care, or had severe disease was lower in the Omicron wave than in the other three waves.[159] In their review of COVID-19 infection in children before and after Delta and Omicron variants, Khemiri et al report that these variants affected a large proportion of the younger population with presenting signs and symptoms generally similar to the original virus. After the emergence of the Delta and Omicron variants the available information reported high hospitalization rates among children; nevertheless, clinical outcomes were similar or less severe compared to those in children infected before the emergence of these variants.[121]

In South Africa, significantly fewer hospitalized patients required oxygen therapy, mechanical ventilation, or intensive care during the Omicron wave than in previous waves of the pandemic.[29] When compared to those who were hospitalized with the Delta variant (4,852 hospitalizations between July 1, 2021-December 18, 2021), those hospitalized with Omicron (829 hospitalizations between December 19, 2021-January 31, 2022) had a shorter length of stay (median 4 days v. 5 days, p<0.001), were less likely to be admitted to the ICU (16.8% v. 24.2%, p<0.001) and were less likely to receive invasive mechanical ventilation (7.6% v. 13.6%, p<0.001), based on data from COVID-NET.[34]

Mortality

According to a 2020 meta-analysis of paediatric studies published through October 2020, the mortality for paediatric patients 0.1-2%.[35,105] 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.[160]

Mortality data are 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.

In the US, as of 03 January 2023, the mortality was 1,118,484 deaths (334 per 100,000 people). Mortality in the US was higher than that of the UK (290 per 100,000).[4]

Overall reported mortality among hospitalised COVID-19 patients varies from 12.8% to 26% in the EU, US and UK.[41,43 161,162] Mortality rates are declining over time, presumably due to an improved understanding of COVID-19 and its management.[162] In the US, patients hospitalized with the Omicron variant were less likely to die in the hospital than those with the Delta variant (7.0% v. 12.6%, $p<0.001$).[34]

Two recent publications (published prior to availability of the vaccine) describe efforts to develop models to predict mortality of patients with COVID-19. The first, by Vagliano et al, described and validated a predictive model, using data from electronic health records, for in-hospital mortality of 972 COVID-19 patients admitted between 15 February 2020 and 1st January 2021 to the intensive care units of 19 hospitals during two different waves of the pandemic. In total 322 patients (33.1 %) died during their hospital stay. Survivors were significantly younger (61.0 vs 68.2 years) and were less often males (69.8 % vs 77.6 %) than non-survivors. The strongest risk factors for mortality in the final model were older age, higher average fraction of inspired oxygen in the first 24 hours of admission, and higher maximum glucose in the first 24 hours of admission. A lower estimated glomerular filtration rate in first 24 hours of admission and higher neutrophil count in the first 24 hours of admission were other important risk factors for death.[163]

The second, by Sozio et al, was an observational, retrospective study that examined patients ≥18 years old with confirmed (by real-time reverse-transcription PCR) COVID-19 presenting to the Emergency Departments of 10 hospitals in the United Kingdom, Italy, Spain, and Switzerland, predominantly during the first wave of the pandemic. The individual probability of being discharged directly from ED or of being admitted to hospital, with or without risk of mortality due to COVID-19, was estimated with several different implementations of machine learning models based on multiclass random forest classifiers. Analysis of Variance testing was performed according to admission and outcome status (not admitted, admitted and survived, admitted and died). Those patients who were admitted and died were older, more likely male, had higher serum creatinine levels, had lower platelet counts, had higher levels of mid-regional pro-adrenomedullin (MR-proADM; an inflammatory biomarker that improves the prognostic assessment of patients with sepsis, septic shock and organ failure), higher white blood cell counts, lower lymphocyte counts, higher LDH, Procalcitonin, CRP and D-dimer levels, and more often had comorbidities including cardiovascular disease, respiratory disease, chronic kidney disease, diabetes, hypertension, and malignancy.

The most important predictors of admission and death were in order of strength: MR-proADM, age, LDH level CRP level, WBC count and platelet count. The authors presented a decision tree to facilitate interpretation of the most important interactions captured by the random forest classifier, in which age represents the predominant risk factor in determining the need for hospitalization, which is further enhanced by the patient's levels of MR-proADM and CRP.[23]

The latest XBB.1.5 risk assessment report in June 2023 from the WHO reported lower number of deaths in hospitals compared to other Omicron variants, indicating low risk of XBB.1.5 variant.[164]

There is currently no evidence of increased mortality with XBB.1.5. relative to that of previously circulating Omicron sub-lineages; however, like other omicron variants, mortality rates are lower as compared to Delta. A preliminary CDC analysis of cases in New York City that occurred November–December 2022 found that patients infected with XBB.1.5 were generally younger, more likely to be Hispanic or Black, and more likely to live in high-poverty neighborhoods compared to those infected with BQ.1. However, there was no difference in the number of deaths per hospital admissions of patients with XBB.1.5 compared to BQ.1.[126] Data reported out of England's Office of National Statistics found that the risk of death involving COVID-19 was 67% lower (hazard ratio: 0.33, 95% confidence interval: 0.24 to 0.45) following Omicron infection relative to Delta.[165] The difference in risk of death varied by age and sex, with the reduction in risk greater in those aged 59 years or younger and in males. Similar to hypotheses for more mild symptom profiles in XBB.1.5, prior exposure to vaccine and/or infection and decreased virulence might underlie mortality risk.

Complications of COVID-19 and Long-COVID

Complications of COVID-19 include impaired function of the heart/cardiovascular system,[166-169] brain/neurological system,[167,168] lung, gastrointestinal/hepatobiliary system,[169] kidney,[170,171] metabolic/endocrine systems,[172] and coagulation system.[173-175]

Complications affecting the heart/cardiovascular system that have been observed include acute myocardial injury, acute coronary syndromes, venous and arterial thrombosis, cardiomyopathy, arrhythmia, myocarditis, pericarditis, heart failure, pulmonary hypertension, and right ventricular dysfunction.[176] One recent review reports that the proportions of patients experiencing some of these complications are as follows: cardiac dysrhythmias in 17 to 44%, cardiac injury with increases in blood troponin in 22 to 40%, myocarditis in 2 to 7%, heart failure in 4 to 21%, and thromboembolic events in 15 to 39%.[177] Another recent review indicates that injury to the myocardium has been reported in up to 30% of hospitalized COVID-19 patients and up to 55% in those with pre-existing cardiovascular disease.[178] In addition, it has been reported that long-term follow-up of Covid-19 patients has revealed increased incidence of arrhythmia, heart failure, acute coronary syndrome, right ventricular dysfunction, and myocardial fibrosis.[176]

Neurologic complications of Covid-19 infection have also been extensively studied. Dimitriadis et al examined neurologic manifestations in critically ill Covid-19 patients in a prospective, multicenter, observational registry study of such patients admitted to 19 German ICUs between April 2020 and September 2021. During the study period, among the 15 ICUs that reported a total of 2681 admissions, 340 patients (12.7%) developed neurologic manifestations, the most common being encephalopathy (including delirium, disorder of consciousness, hypoxic encephalopathy, encephalopathy not further described), cerebrovascular disorders (including ischemic stroke, intra-cerebral haemorrhage, subarachnoid haemorrhage, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, cerebral venous sinus thrombosis, cerebral microbleeds, subdural hematoma) and neuromuscular disorders (including polyneuropathy or myopathy, Guillain–Barré syndrome, myasthenia, myositis).[167]

A meta-analysis on the incidence of seizures among Covid-19 patients by Hussaini et al included a total of 11,526 patients from 21 published articles. A total of 255 (2.2%; 95% CI 0.05-0.24, $p < 0.01$) patients presented with seizures as the first manifestation of COVID-19. Only 71 of the 255 patients had previously been diagnosed with epilepsy.[168]

A systematic review by Sourani A et al.[179] reported that 71.4% of COVID-19 patients from seven datasets, presented with spinal epidural hematoma (EDH) Of them, three patients were treated conservatively, while four received neurosurgical intervention. Also, patients with pain and sensorimotor deficits responded fully to the given treatment (100%). However, no response was observed by the sphincter to the given treatment (0%). Long-term follow-up resulted in a good recovery in 71% of patients. SARS-CoV-2-associated spontaneous spinal haemorrhage is a rare complication of infection, with an often-insidious presentation that requires high clinical suspicion.

Another rare infection[180] in COVID-19 patients included mucormycosis. The overall mortality rate in COVID-19–associated mucormycosis patients was found to be 38.9%.

There are also psychological complications of Covid-19 infection.

Khraisat et al conducted a meta-analysis to estimate the pooled prevalence of mental disorders among COVID-19 survivors. The analysis included 27 studies with a total sample size of 9605 Covid-19 survivors. The prevalence rates (95% CI) for psychological complications were as follows: overall psychological distress 36% (22–51%), post-traumatic stress disorder 20% (16–24%), anxiety 22% (18–27%), depression 21% (16–28%), and sleeping disorders 35% (29–41%).[181] Also, a recent narrative review of the literature on post-acute neurologic sequelae of COVID-19 indicates that common conditions include persistent fatigue, headaches, “brain fog”, depression, and anxiety.[182]

Shih et al reported that patients with COVID-19 can have GI and hepatobiliary manifestations, which are often mild and transient, although they can occasionally be severe. The most common consequential GI manifestation is ischemic enterocolitis. Abnormal liver chemistries occur in 14-53% of Covid-19 patients, both at admission and during hospitalization. Typically, liver function test elevations are mild and recover without specific treatment. Rarely patients with COVID- 19 may present with acute liver failure, develop primary liver disease during their illness, or develop post- COVID-19 cholangiopathy (a form of secondary sclerosing cholangitis).[169]

Mallhi et al performed a review of 42 published systematic reviews on Covid-associated acute kidney injury (CAKI). They found that the incidence of CAKI ranged from 4.3% to 36.4% overall among COVID-19 patients, 36%–50% in kidney transplant recipients (KTRs), and up to 53% in patients with severe or critical illness.[170] Matsumoto and Prowle in their review of the literature on CAKI report that large observational studies and meta-analyses report an AKI incidence of 28-34% in all inpatients and 46-77% in patients admitted to the ICU. The majority of survivors recovered their kidney function by hospital discharge; however, they remained at increased risk of future AKI, a decline in estimated glomerular filtration rate (eGFR), and chronic kidney disease. Moreover, even in the absence of overt AKI a significant proportion of survivors of COVID-19 hospitalisation had reduced eGFR on follow-up.[171]

The risk of new onset diabetes mellitus was reported to be 66% (95% CI 1.38; 2.00) higher among survivors of COVID-19 compared with controls in a meta-analysis of eight studies consisting of 4,270,747 COVID-19 patients and 43,203,759 controls.[172]

Other complications of COVID-19 include hemolytic anemia,[183] endocrine disorders (including the thyroid, pancreas, adrenal, neuroendocrine, gonadal, and parathyroid glands) [184,185], musculoskeletal disorders including persisting or new-onset fatigue, myalgia, arthralgia, arthritis, muscle weakness,[186] opportunistic infections,[89] and adverse pregnancy outcomes including preterm labour and caesarean delivery without any intrauterine infection, and severe neonatal asphyxia.[187]

A recent narrative review of coagulopathy associated with Covid-19 infection indicates thrombosis occurs as a result of the virus invading endothelial cells causing local complement activation and inflammation which leads to microvascular thrombi (both venous and arterial), which may eventually lead to widespread macrovascular thrombotic injury and in some cases end-organ failure.[174]

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.[188]

Complications of COVID-19 in pediatric populations

In children, multisystem inflammatory syndrome has been observed to be temporally associated with COVID-19 infection and often develop a rash following resolution of COVID-19.[105,189,190] Complications include coronary artery aneurysms, cardiac dysfunction, and multiorgan inflammatory manifestations with similarities to Kawasaki disease and other inflammatory conditions. Neonates born to mothers with SARS-CoV-2 infection during pregnancy have also demonstrated a multisystem inflammatory syndrome with raised inflammatory markers and multi-organ dysfunction, especially of the heart.[191]

As of 03 January 2023, there were 9,333 cases of MIS-C reported to health departments in the United States with 76 deaths reported among those who met the MIS-C case definition.[192] Additional symptoms of MIS-C include abdominal pain, bloodshot eyes, chest tightness or pain, diarrhoea, lethargy, headache, low blood pressure, neck pain, and vomiting.[193]

A recent narrative review of thromboembolic events (TEs) as complications of COVID-19 in children used data from 62 studies, describing 138 patients. Venous TEs represented the majority (54%), followed by arterial thrombosis (38%, mainly arterial ischemic stroke), and intra-cardiac thrombosis (8%). Within the venous TEs group, pulmonary embolism was the most frequent, followed by deep venous thrombosis, central venous sinus thrombosis, and splanchnic venous thrombosis.[194] A systematic review with meta-analysis of four studies to determine the incidence of thrombotic events in children and adolescent patients with COVID-19 infection reported that among 1,128 COVID-19 positive pediatric patients, nearly half of them developed inflammatory sequelae and 7.35% had thrombotic events.[195]

Recent studies have also shown that paediatric patients with COVID-19 are at increased risk of diabetes mellitus, particularly in the 30 days after their COVID-19 infection.[196,197]

Complications of Long-Covid

COVID-19 symptoms can persist weeks or months beyond the acute infection.[198,199]
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).[199]

A meta-analysis of 31 studies published until September 17, 2020 prior to the emergence of the Omicron variant 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%).[200]

Yang et al conducted a meta-analysis of 72 studies with a total of 88,769 patients to examine the occurrence of different symptoms up to one year of follow-up for previously hospitalized patients with COVID-19. A total of 167 sequelae related to COVID-19 were identified, the more common ones being fatigue 27.5%, somnipathy 20.1%, anxiety 18.0%, dyspnea 15.5%, PTSD 14.6%, hypomnesia 13.4%, arthralgia 12.9%, depression 12.7%, alopecia 11.2%. The prevalence of most symptoms declined after > 9 months of follow-up, but fatigue and somnipathy persisted in 26.2% and 15.1% of patients, respectively.[201]

The incidence of Long Covid progressively increases from non-hospitalized to hospitalized individuals to those hospitalized and treated in the ICU. It varies from 16 and 53% of patients and occurs more frequently in patients after infection with the Alpha or Delta variants in comparison with patients infected with the Omicron variant.[177] Major organ damage post-discharge among adults hospitalized for COVID-19, including incident cardiac, pulmonary, liver, acute and chronic kidney, stroke, diabetes, and coagulation disorders were consistently greater in adults hospitalised for COVID-19 compared with non-COVID-controls in a meta-analysis of nine studies with follow-up of patients ranging from 4 to 22 weeks post-discharge.[202]

Cardiovascular sequelae in post-acute COVID-19 include dyspnoea, chest pain, sinus bradycardia / dysrhythmias, palpitations and/or tachycardia, cerebrovascular disorders, pericarditis, myocarditis, ischemic heart disease, heart failure, thromboembolic events, right ventricular dysfunction, myocardial fibrosis, hypertension, 1 year.[166,176,177]

Pulmonary symptoms and complications seen in long Covid include dyspnoea (occurring in 15% of non-hospitalized patients and up to 81% of previously hospitalized patients), cough, chest pain, or decreased exercise tolerance.[203]

A systematic review and meta-analysis assessed the long-term neurocognitive effects of COVID-19 in three studies comprised of 3,304 post-COVID-19 patients. Persistent neurological / cognitive sequelae of Covid-19 infection included headache 27.8%, fatigue 26.7%, myalgia 23.14%, anosmia 22.8%, dysgeusia 12.1%, sleep disturbance 63.1%, confusion 32.6%, difficulty concentrating 22%, and psychiatric symptoms like PTSD 31%, feeling depressed 20%, and suicidality 2%.[204]

Dangayach et al reports in a narrative review of the literature that neurologic complications in post-acute COVID-19 range from persistent fatigue, headaches, "brain fog", depression, anxiety, and postural orthostatic tachycardia even in patients with mild disease.[182]

Musculoskeletal disorders with long COVID, including persisting or new-onset fatigue, myalgia, arthralgia, arthritis, and muscle weakness, were noted in review of systematic reviews and meta-analyses that included 24 studies.[186]

Complications of Long-Covid in paediatric populations

It has been estimated that up to 25% of the >14,000,000 children with COVID-19 in the year 2019 have developed persistent symptoms of fatigue, post-exertional malaise, neurologic and cognitive symptoms, and other symptoms that interfere with activities of daily living for months after their initial illness; however more recent data suggest that the proportion of paediatric COVID-19 patients with long-term sequelae/symptoms is in the range of 3-10%.[205]

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.[100,206,207]

Pellegrino et al performed a systematic literature review up to 15 February 2022 to summarize long COVID evidence and to assess prevalence and clinical presentation in children and adolescents. Twenty-two articles were included; 9 studies provided a control group. The authors found high variability in terms of prevalence (1.6–70%). The most frequently reported symptoms were fatigue (2–87%), headache (3.5–80%), arthro-myalgias (5.4–66%), chest tightness or pain (1.4–51%), and dyspnoea (2–57.1%). Five studies reported limitations in daily function due to long COVID; most studies did not detect evidence of long-term pulmonary sequelae in these patients.[208]

Important co-morbidities:

As mentioned previously, there are a number of common comorbidities in patients with COVID-19; many of these conditions are also associated with more severe disease or progression of disease.

Important comorbidities in those with more severe disease/hospitalised COVID-19 patients include hypertension, diabetes, obesity, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease or asthma, chronic kidney disease, cancer, chronic liver disease and autoimmune disease.[22,37-39,52,68,77,78,81-85,143,147,150]

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 12 using TESSy data posted on 12 August 2021 below.[209]

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

	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 13 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.[45]

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 13. 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

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%).[49] 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.[46] 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%).[46]

A recent systematic review and meta-analysis using published reports through August 25, 2021 revealed that prematurity in young infants (RR, 2.00; 95% CI, 1.63-2.46), obesity (RR, 1.43; 95% CI, 1.24-1.64), diabetes (RR, 2.26; 95% CI, 1.95–2.62), chronic lung disease (RR, 2.62; 95% CI, 1.71-4.00), heart disease (RR, 1.82; 95% CI, 1.58-2.09), neurologic disease (RR, 1.18; 95% CI, 1.05-1.33), and immunocompromised status (RR, 1.44; 95% CI, 1.01–2.04) were significant comorbidities associated with severe COVID-19 (intensive care unit admission, invasive mechanical ventilation, and/or death) in children.[210]

Crossfield et al performed a population-based prospective study linking individual genetic, biomarker, survey and electronic health record data from >500 000 UK participants, aged 40–69 years at recruitment (2006– 2010). The study used individual patient-level data from the UK BioBank database, linked to COVID-19 data sets from laboratories, hospitals, and death certificates. The study population included those who provided baseline assessment data, were alive at the start of the study period and had not withdrawn consent. All subjects had a COVID-19 diagnosis by a positive laboratory test result, or an ICD-10 code U071 or U072 recorded in hospital or death certificate data. A cohort of 9560 patients with COVID-19 of whom 50.8% (n=4,860) were women and 7,274 (76.1%) were White European were included. The most common comorbidities of the study population included cardiovascular disease (12.8%), chronic respiratory disease (15.5%), chronic kidney disease (0.8%), diabetes (7.1%), hypertension (28.6%), chronic liver disease (0.3%), and neurological disease (2.3%). The total number of comorbidities per subject was 0: 52.7%; 1: 31.7% and ≥2: 15.6%.[68]

Alharbi et al conducted a retrospective, cross-sectional observational of patients in a COVID-19-designated specialty hospital in Saudi Arabia. Over an 11-month period from March 2020 to January 2021, corresponding to the first wave of infection in the country when therapeutic interventions had limited options and were mostly dependent on a given patient's condition. A total of 619 patients' records (non-ICU = 369 and ICU = 250 patients, 61.4% male, 6.3% age 0-20 years, 16.8% age 21-40, 27.9% age 41-60, and 48.9% age >60) with confirmed COVID-19 diagnosed with a real-time PCR assay for SARS-CoV-2 were included. The most common comorbidities of the study population included hypertension (59.8%), diabetes (47.2%), chronic pulmonary disease (28.6%), heart failure (13.2%), coronary artery disease (4.8%), and cancer (2.7%).[148]

A prospective observational study of hospitalized patients with confirmed SARS-CoV-2 infection by reverse transcription-polymerase chain reaction and treated with advanced respiratory support (including high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation) during the first two years of the pandemic was conducted by Reyes et al. Included were a total of 66,565 patients from five continents (63.5% male, 82.6% hospitalized and treated in high-income countries, 78.2% hospitalized and treated in Europe, 44.0% between 60 and 80 years old) were included. The most common comorbidities of the study population included arterial hypertension (41.3%), diabetes mellitus (30.3%), chronic cardiac disease (not hypertension; 22.1%), asthma (12.2%), chronic kidney disease (11.3%), obesity (16.2%), chronic pulmonary disease (not asthma; 13.3%), rheumatological disorder (8.1%), malignant neoplasm (7.7%), chronic neurological disorder (7.4%), and dementia (6.0%).[211]

Ozonoff et al conducted a prospective, observational study of hospitalized patients with COVID-19 from 20 hospitals (affiliated with 15 academic institutions) across the US. Symptomatic patients ≥18 with confirmed positive SARS-CoV-2 PCR were enrolled within 48 hours of hospital admission. Hospital admission data collected up to 11 November 2021 was analyzed. Between 05 May 2020 and 19 March 2021, 1,164 patients enrolled in the study and who met eligibility criteria were included in the final analysis. The median age of the study population was 59 years (interquartile range 20), 61% were men, and 32% smoked or used vaporized nicotine products.

The most common comorbid conditions included hypertension 58%, diabetes 37%, chronic lung disease (not asthma) 20%, asthma 15%, chronic cardiac disease 27%, chronic kidney disease 15%, chronic liver disease 5%, chronic neurologic disorder 12%, organ transplantation 5%, malignancy 10%, drug, or alcohol abuse 8%, class 1-2 obesity (BMI=30-39.9) 41%, class 3 obesity (BMI=40+) 14%.[22]

Lastly, an observational study of all COVID-19 patients admitted to 19 Dutch ICUs participating in both the national quality registry National Intensive Care Evaluation and the EHR-based Dutch Data Warehouse as conducted by Vagliano et al. A total of 1,533 patients from the EHR and 1,563 from the registry were included. Subjects were ≥18 years old and were admitted between 15 February 2020 and 01 January 2021 with confirmed COVID-19 by positive real-time reverse transcriptase polymerase chain reaction assay for SARS-CoV-2 or, in the early phase of the pandemic, with a CT-scan consistent with COVID-19. The authors developed multiple models on data from the first 24 hours of ICU admissions from February to June 2020 (first wave) and validated the models on prospective patients admitted to the same ICUs between July and December 2020 (second wave). The authors reported the prevalence of the following comorbidities during the first and second waves, respectively, as follows: acute renal failure (9.5% and 9.3%), chronic obstructive pulmonary disease failure (9.5% and 9.1%), chronic respiratory insufficiency (3.2% and 2.0%), diabetes (21.5% and 26.9%).[163]

With respect to comorbidities among persons infected with the Omicron variant, little published data was found. A study using data from 17 of 18 regional health agencies in France examined the demographic characteristics of 468 confirmed cases of the Omicron variant from 23 November 2021 to 11 January 2022. The cases were of a median age of 35 years, and 55% were female. Among the 278 cases in whom the information was known, 39 (14%) had been previously infected with Covid-19. Among the 394 cases with data on vaccination status, 92 (23%) were unvaccinated, 254 cases (64%) had received 2 doses of vaccine and 28 cases (7%) had received 3 doses.[26] Only 16% had pre-existing conditions (hypertension, obesity, diabetes, chronic respiratory disease, renal insufficiency, cancer, immunosuppression, liver disease, heart disease, neuromuscular condition, other condition, or pregnancy). The prevalence of the individual comorbidities was not reported by the authors.[26] It is possible that the low rate of comorbidities in this study population is driven by the relatively low age of the patients studied.

In the US (Virginia), data were collected from electronic medical records of adults (≥18 years) with a diagnosis of COVID-19 (ICD-10 code U07.1) hospitalized in a single health care system from 05 March 2020 to 05 February 2022 to evaluate hospitalized patients with COVID-19.[28] The healthcare system includes five hospitals in Virginia with a total of 1,800 licensed acute care beds. The study period was constructed based on the most prevalent SARS-CoV-2 variant at the time as follows: March 2020 - June 2021 (pre-Delta), July - November 2021 (predominantly-Delta), and December 2021 - February 2022 (predominantly-Omicron). The prevalence of most common comorbidities of the study population, stratified by the variant that was predominant at the time of patient admission are shown in Table 14.[28]

Table 14. Prevalence (%) of most common comorbid conditions among patient hospitalized for COVID-19 in a single health care system from March 5th, 2020, to February 5th, 2022, by predominant variant at the time of admission

	Pre-Delta	**Delta**	**Omicron**
	n=7112	n=860	n=1556
Obesity (BMI > 30)	43.4	43.3	38.0
Morbid obesity (BMI > 40)	8.5	8.9	8.6
Myocardial infarction	8.5	13.4	14.5)
Congestive heart failure	14.9	20.9	25.1
Peripheral vascular disease	10.5	13.0	16.3
Cerebrovascular disease	12.6	16.2	17.9
Dementia	12.4	12.3	16.1
Chronic pulmonary disease	21.3	24.9	29.4
Mild liver disease	9.5	11.2	11.1
Diabetes without complications	21.7	16.2	13.9
Diabetes with complications	15.5	20.0	23.2
Renal disease	19.7	24.5	31.5
Non-metastatic cancer	5.0	7.0	8.4

Chen X, et al performed an observational cohort study of hospitalized patients confirmed with SARS-CoV-2 during the 2022 Omicron wave in Shanghai, China. Eligible patients were required to be ≥18 years old with confirmed SARS-CoV-2 infection by real-time PCR between Mar 20 and May 10, 2022. Data on all enrolled participants were obtained from the hospital information system at which they were admitted. A total of 847 eligible patients were included in the study (age >70 years 30.3%, not fully vaccinated 55.8%, 0 comorbidities 34.6%, 1 comorbidity 25.9%, 2 comorbidities 24.1%, ≥3 comorbidities 15.5%, long-term bedridden 19.0%). The most common reported comorbidities were heart conditions 30.3%, metabolic disease 18.5%, chronic kidney disease stage 4–5 (glomerular filtration rate <30 ml/min) or required dialysis 18.4%, isolated hypertension 17.1%, cancer 12.5%, cerebral vascular disease 7.3%, and lung disease 7.3%.[153]

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 was also completed. No additional toxicity studies are planned for COVID-19 mRNA vaccine. Mouse immunogenicity studies were also conducted with variant modified vaccines.

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.[212] 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.[213] 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. Variant-modified vaccines (BNT162b2 Beta, BNT162b2 Omicron BA.1, and BNT162b2 Omicron BA.4/BA.5) evaluated either as monovalent formulations or also as bivalent formulations (Original + Variant) elicited robust neutralizing antibody responses in mice. Responses were generally highest against the variant matched to the vaccine; bivalent formulations provided a greater breadth of the antibody response in naïve mice compared to monovalent formulations. When administered as a 3rd dose booster to mice that received 2 prior doses of BNT162b2, Omicron BA.4/BA.5 variant vaccines elicited a more balanced response against Omicron sublineages compared to a booster with an Omicron BA.1 variant vaccine.

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 ALC0159, 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 ALC0159. Further studies indicated- metabolism played a role in the elimination of ALC0315. -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 LNPformulated 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.[214]

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[215] 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.[216] 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 15. There was no evidence of vaccine-elicited disease enhancement.

Table 15. 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 LNPsiRNA pharmaceutical Onpattro[215], 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. 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

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 was 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 C4591001 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 C4591001 evaluated 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 are anticipated to bridge to the 16- to 25-year-old cohort.

Booster groups were subsequently added to evaluate boostability and protection against variant virus strains.

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. In study C4591001, the total follow-up time from Dose 1 to unblinding for the 21,926 participants in the vaccine group was 83.4 person-year and for the 21,921 participants in the placebo group was 82.2 person-years.

The efficacy analysis in the 12 years and older population for the primary series, the analysis of 6-month post dose 2 data in the 16 years and older population and the evaluation of booster effects and/or protection against emerging SARS-CoV-2 variants of concern, in participants 18 to 55 years of age have been reported out in previous RMPs. Refer to Annex 7 for CT exposure.

Analysis of 6-month post Dose-3 data was conducted on 12 to 15 years of age who received the BNT162b2 booster at the cut-off on 03 November 2022. Clinical trial exposure tables are provided in Annex 7 (Table 28 to Table 30).

Further evaluation for the paediatric population (5-<12 years of age) has been conducted in study C4591007 (see Annex 7 from Table 31 to Table 38).

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 was planned to evaluate BNT162b2 2-doses separated by 21 days 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.

The study design was modified (Amendment 6) to provide the necessary safety and immunogenicity data to support an EUA and future licensure of a 3rd dose of BNT162b2 to maximize the protection against variants of concern including Delta and Omicron as seen in real-world vaccine effectiveness in older age groups.

Exposure to the 3rd dose of BNT162b2 for participants aged 5 to <12 years of age by demographic characteristics is shown in Annex 7 (Table 39 and Table 40). In addition, exposure in special population for participants 5 to <12 years of age who received a 3rd dose is shown in Annex 7 (Table 41).

Further evaluation for the paediatric population (from the 2 to <5 years and 6 months to <2 years of age) has been conducted in study C4591007 (which remains ongoing).

As of the cut-off date of 16 July 2021, a total of 48 participants (6 months to < 2 years [16], 2 years to <5 years [32]) in Phase 1 were vaccinated in the BNT162b2 clinical development program.

Exposure to BNT162b2 for participants aged 6 months to < 2 years of age and 2 years to <5 years of age by number of doses and demographic characteristics for Phase 1 are shown in Annex 7 (Table 42 to 47). Exposure in special populations for participants aged 2 years to <5 years of age is shown in Table 48.

As of the cut-off date of 29 April 2022, a total of 3013 Phase 2/3 participants (6 months to < 2 years [1178], 2 years to <5 years [1835]) were vaccinated in the BNT162b2 clinical development program in the blinded placebo controlled follow up period.

Exposure for Phase 2/3 Blinded Placebo-Controlled Follow-up Period are shown in Annex 7 Table 49 to Table 53. In addition, Phase 2/3 exposure in special populations for participants aged 6 months to < 2 years of age and 2 years to <5 years of age are shown in Table 54 and Table 55.

A total of 650 participants received BNT162b2 vaccine in the open-label follow-up period after the unblinding in participants who originally received placebo and then received BNT162b2.

A total of 76 participants who turned 5 years of age then received BNT162b2 at the age-appropriate dose level of 10 µg.

As regards exposure for the Open-Label Follow-up Period – Participants who originally received Placebo and then received BNT162b2 after unblinding are shown in Annex 7 from Table 56 to Table 60. In addition, Phase 2/3 exposure in special populations for participants aged 6 months to < 2 years of age and 2 years to <5 years of age are shown in Table 61 and Table 62.

A total of 687 participants received BNT162b2 in the open-label follow-up period who originally received BNT162b2. A total of 121 participants who turned 5 years of age then received BNT162b2 at the age-appropriate dose level of 10 µg.

As regards to exposure for the Open-Label Follow-up Period – Participants who originally received BNT162b2 are shown in Annex 7 from Table 63 to Table 67. In addition, Phase 2/3 exposure in special populations for participants aged 6 months to < 2 years of age and 2 years to <5 years of age are shown in Table 68 and Table 69.

Combined exposure for Phase 2/3, 6 months post dose 3, for participants aged 6 months to < 12 years who received original BNT162b2 and participants who were randomized to placebo and received BNT162b2 after unblinding is reported in Annex 7, from Table 70 to Table 81.

Evaluation of boosting dose(s) - Study C4591031

Clinical data in approximately 1840 participants >55 years of age from ongoing C4591031 Substudy E (BNT162b2-experienced participants), including safety and immunogenicity data up to 1 month after receipt of a single dose (Dose 4) of BNT162b2 (30 or 60 µg), monovalent BNT162b2 OMI (30 or 60 µg), or bivalent BNT162b2 + BNT162b2 OMI (30 or 60 µg) are provided.

Exposure specific for BNT162b2 (30 µg), monovalent BNT162b2 OMI (30 µg), and bivalent BNT162b2 + BNT162b2 OMI at 30 µg (15 µg each) from substudy E is shown from Table 16 to Table 21.

In addition, clinical data from approximately 640 participants ≥18 to ≤55 years of age from ongoing Study C4591031, Substudy D (Cohort 2: BNT162b2-experienced participants), including safety and immunogenicity to 1 month after receipt of an additional booster (fourth) dose of an Omicron variant specific vaccine, BNT162b2 OMI 30 µg are provided. These data are derived from participants who were originally randomized to the active vaccine group in Phase 3 of registrational Study C4591001 and completed the original BNT162b2 30-µg two-dose primary series, then enrolled into Study C4591031, Substudy A, and were randomized to receive a third (booster dose) of BNT162b2 30 µg or placebo ≥6 months after receiving Dose 2.

Exposure for BNT162b2 30-µg and the Omicron variant specific BNT162b2 OMI 30 µg from Substudy D is shown from Table 22 to Table 25.

Study C4591031, Substudy C (SSC) evaluated booster dosing at BNT162b2 at 30 µg and 10 µg dose levels in healthy individuals 12 through 17 years of age who completed a 2-dose primary series of BNT162b2 (30 µg) at least 5 months prior to study randomization. The 1-month post dose 3 results are provided from Table 26 to Table 29.

Exposure to bivalent BNT162b2 (original/Omi BA.4/BA.5)- Study C4591044 (12 years of age and older)

Study C4591044 evaluated a dose of bivalent BNT162b2 (original/Omi BA.4/BA.5) at 30 µg and 60 µg in individuals 12 through 17 years (30 µg only) and individuals 18 years of age and older who completed 3 doses of BNT162b2 (30 µg) at least 150 to 365 days prior to study randomization. The results are provided from Table 30 to Table 35.

Exposure to bivalent BNT162b2 (original/Omi BA.4/BA.5) - Study C4591048 (6 months -11 years of age)

Study C4591048 evaluated a dose of bivalent BNT162b2 (original/Omi BA.4/BA.5) at 3 µg in individuals 6 months to <5 years of age (sub-study B, Group 2) and at 10 µg in individuals 5 to <12 years of age (sub-study D Group 2) who completed 3-doses of BNT162b2 (3 or 10 µg) at least 60 to 240 days prior to study randomization.

The results are provided from Table 36 to Table 40 (SSB) and from Table 41 to Table 44 (SSD).

Ongoing[3] Pfizer-BioNTech COVID-19 mRNA vaccine interventional clinical studies also include:

- C4591015[4,5] 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.

- C4591024[5]: A phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age.

- 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.

<u>Population for analysis of CT data in this RMP includes the following 6 trials:</u>

- 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 COVID19 using different dosing regimens in healthy and immunocompromised adults.

- 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

[3] Studies C4591005, C4591017, C4591020, C4591030 and BNT162-03, BNT162-04, BNT162-06 were completed and therefore are removed from this list.

[4] 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.

[5] This study has completed. Final CSR has not yet been submitted.

safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children and young adults.

- C4591031: Phase 3 master study to evaluate BNT162b2 boosting strategies in healthy individuals previously vaccinated with BNT162b2. Each substudy design is detailed separately and these substudies may be conducted in parallel, as required by the clinical plan, within the framework of this master protocol.
- C4591044: An interventional, randomized, active-controlled, phase 2/3 study to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b RNA based vaccine candidates as a booster dose in COVID 19 vaccine experienced healthy individuals.
- C4591048: A master phase 1/2/3 protocol to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b2 RNA based vaccine candidate(s) in healthy children.

Participants >55 years of age (C4591031 Substudy E)

Clinical study exposure for the >55 years of age is provided from the ongoing C4591031 Substudy E at the cut-off of 05 April 2022 (Sentinel cohort) and at the cut-off date 16 May 2022 (Expanded cohort). Participants who had received 3 doses of BNT162b2 30 µg received a 4th (additional booster dose) of BNT162b2 vaccine, monovalent BNT162b2 OMI or bivalent BNT162b2 + BNT162b2 OMI.

Table 16. Exposure to Study Vaccine (C4591031 Substudy E) – Sentinel and Expanded Cohorts – Participants >55 Years of Age

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses	Number of Subjects Exposed to BNT162b2 OMI	Total Number of Vaccine Doses	Number of Subjects Exposed to BNT162b2 + BNT162b2 OMI	Total Number of Vaccine Doses
> 55 years Vaccine 30 µg Booster dose	325	325	327	327	325	325

Note: Sentinel and expanded cohorts are included.
Note: Participants >55 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose 5-12 months prior to enroll in this substudy were included.
[redacted] SDTM Creation: 27MAY2022 (12:48) Source Data: adsl Table Generation: 12JUL2022 (23:00)
(Data Cutoff Date: Sentinel [05APR2022]/Expanded[16MAY2022]) Output File: ./nda2 ube/C4591031 E PVP/adsl s912

Table 17. Exposure to Study Vaccine by Age Group (C4591031 Substudy E) – Sentinel and Expanded Cohorts – Participants >55 Years of Age

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses	Number of Subjects Exposed to BNT162b2 OMI	Total Number of Vaccine Doses	Number of Subjects Exposed to BNT162b2 + BNT162b2 OMI	Total Number of Vaccine Doses
>55 years to ≤64 years Vaccine 30 µg Booster dose	132	132	126	126	113	113
≥65 years to ≤74 years Vaccine 30 µg Booster dose	154	154	156	156	165	165
≥75 years to ≤84 years Vaccine 30 µg Booster dose	36	36	45	45	45	45
≥85 years Vaccine 30 µg Booster dose	3	3	0	0	2	2

Note: Sentinel and expanded cohorts are included.
Note: Participants >55 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose 5-12 months prior to enroll in this substudy were included.
[redacted] SDTM Creation: 27MAY2022 (12:48) Source Data: adsl Table Generation: 12JUL2022 (23:40)
(Data Cutoff Date: Sentinel [05APR2022]/Expanded[16MAY2022]) Output File: ./nda2_ube/C4591031_E_PVP/adsl_s912b

Table 18. Exposure to Study Vaccine by Dose and Gender (C4591031 Substudy E) – Sentinel and Expanded Cohorts – Participants >55 Years of Age

	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses		Number of Subjects Exposed to BNT162b2 OMI		Total Number of Vaccine Doses		Number of Subjects Exposed to BNT162b2 + BNT162b2 OMI		Total Number of Vaccine Doses	
Dose Age Group	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Vaccine 30 µg >55 years	157	168	157	168	160	167	160	167	175	150	175	150
Total	157	168	157	168	160	167	160	167	175	150	175	150

Note: Sentinel and expanded cohorts are included.
Note: Participants >55 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose 5-12 months prior to enroll in this substudy were included.
[redacted] SDTM Creation: 27MAY2022 (12:48) Source Data: adsl Table Generation: 12JUL2022 (23:40)
(Data Cutoff Date: Sentinel [05APR2022]/Expanded[16MAY2022]) Output File: ./nda2 ube/C4591031 E PVP/adsl s931

Table 19. Exposure to Study Vaccine by Dose, Age Group and Gender (C4591031 Substudy E) – Sentinel and Expanded Cohorts – Participants >55 Years of Age

	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses		Number of Subjects Exposed to BNT162b2 OMI		Total Number of Vaccine Doses		Number of Subjects Exposed to BNT162b2 + BNT162b2 OMI		Total Number of Vaccine Doses	
Dose Age Group	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Vaccine 30 µg												
>55 years to ≤64 years	62	70	62	70	58	68	58	68	60	53	60	53
≥65 years to ≤74 years	78	76	78	76	74	82	74	82	87	78	87	78
≥75 years to ≤84 years	16	20	16	20	28	17	28	17	26	19	26	19
≥85 years	1	2	1	2	0	0	0	0	2	0	2	0
Total	157	168	157	168	160	167	160	167	175	150	175	150

Note: Sentinel and expanded cohorts are included.
Note: Participants >55 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose 5-12 months prior to enroll in this substudy were included.
[redacted] SDTM Creation: 27MAY2022 (12:48) Source Data: adsl Table Generation: 12JUL2022 (23:40)
(Data Cutoff Date: Sentinel [05APR2022]/Expanded[16MAY2022]) Output File: ./nda2_ube/C4591031_E_PVP/adsl_s932b

Table 20. Exposure to BNT162b2 by Race/Ethnic Origin (C4591031 Substudy E) – Sentinel and Expanded Cohorts – Participants >55 Years of Age

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses	Number of Subjects Exposed to BNT162b2 OMI	Total Number of Vaccine Doses	Number of Subjects Exposed to BNT162b2 + BNT162b2 OMI	Total Number of Vaccine Doses
Vaccine 30 µg						
Racial origin						
White	284	284	276	276	288	288
Black or African American	20	20	25	25	15	15
Asian	16	16	18	18	20	20
Native Hawaiian or other Pacific Islander	2	2	0	0	0	0
Multiracial	3	3	6	6	1	1
Not reported	0	0	2	2	1	1
Total	325	325	327	327	325	325
Ethnic origin						
Hispanic/Latino	58	58	48	48	47	47
Non-Hispanic/non-Latino	267	267	279	279	278	278
Total	325	325	327	327	325	325

Note: Sentinel and expanded cohorts are included.
Note: Participants >55 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose 5-12 months prior to enroll in this substudy were included.
[redacted] SDTM Creation: 27MAY2022 (12:48) Source Data: adsl Table Generation: 12JUL2022 (23:40)
(Data Cutoff Date: Sentinel [05APR2022]/Expanded[16MAY2022]) Output File: ./nda2_ube/C4591031_E_PVP/adsl_s952b

Table 21. Exposure to Study Vaccine by Special Population (C4591031 Substudy E) – Sentinel and Expanded Cohorts – Participants >55 Years of Age

Population	Number of Subjects Exposed to BNT162b2 (30 µg) (N[a]=325) n[b]	Number of Subjects Exposed to BNT162b2 OMI (30 µg) (N[a]=327) n[b]	Number of Subjects Exposed to BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (N[a]=325) n[b]
Subjects with any baseline comorbidity	180	177	173
AIDS/HIV	0	0	2
Any Malignancy + Metastatic Solid Tumor + Leukemia + Lymphoma	30	36	32
Chronic Pulmonary Disease	23	25	31
Renal Disease	6	2	5
Rheumatic Disease	2	2	1
Mild Liver Disease + Moderate or Severe Liver Disease	1	3	2
Cerebrovascular Disease + Peripheral Vascular Disease + Myocardial Infarction + Congestive Heart Failure	19	19	22
Diabetes With/Without Chronic Complication	35	48	47
Hemiplegia or Paraplegia	0	0	0
Peptic Ulcer Disease	1	3	0
Obese	117	115	112

Note: Sentinel and expanded cohorts are included.
Note: Participants >55 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose 5-12 months prior to enroll in this substudy were included.
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: Hemiplegia or Paraplegia only includes preferred terms Hemiplegia and Paraplegia. No participants were identified.

a. N = number of participants in the specified group.
b. n = Number of participants reporting at least 1 occurrence of any comorbidity or obese (BMI ≥30 kg/m2 [≥16 Years of age]).

[redacted] SDTM Creation: 26MAY2022 (22:31) Source Data: admh Table Generation: 12JUL2022 (23:40)
(Data Cutoff Date: Sentinel [05APR2022]/Expanded[16MAY2022]) Output File: ./nda2_ube/C4591031_E_PVP/admh_s953

Participants ≥18 to ≤55 years of age C4591031 Substudy D

Supportive clinical study exposure for individuals ≥18 to ≤55 years of age is provided at the cut-off of 11 Mar 2022, from the ongoing C4591031 randomized Phase 3 study evaluating an additional booster (fourth) dose of BNT162b2 30 µg and the Omicron variant specific BNT162b2 OMI 30 µg to BNT162b2-experienced participants in Cohort 2 who have received 3 doses of BNT162b2.

Table 22. Exposure to Study Vaccine by Age Group (C4591031 Substudy D) – Cohort 2

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2 OMI	Total Number of Vaccine Doses	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥18 years to ≤55 years Vaccine 30 µg Booster dose	315	315	325	325

Note: Only subjects ≥18 years of age to ≤55 years of age who have completed 3 doses of BNT162b2 at least 3-6 months prior to randomization were enrolled in study C4591031 Substudy D Cohort 2 to receive BNT162b2 or BNT162b2 OMI.
[redacted] SDTM Creation: 11APR2022 (01:32) Source Data: adsl Table Generation: 18MAY2022 (12:24)
(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 08APR2022) Output File: ./nda2_ubd/C4591031_D_PVP/adsl_boost_s912

Table 23. Exposure to Study Vaccine by Age Group and Gender (C4591031 Substudy D) – Cohort 2

	Number of Subjects Exposed to BNT162b2 OMI		Total Number of Vaccine Doses		Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses	
Age Group Dose	Male	Female	Male	Female	Male	Female	Male	Female
≥18 years to ≤55 years Vaccine 30 µg	163	152	163	152	168	157	168	157
Total	163	152	163	152	168	157	168	157

Note: Only subjects ≥18 years of age to ≤55 years of age who have completed 3 doses of BNT162b2 at least 3-6 months prior to randomization were enrolled in study C4591031 Substudy D Cohort 2 to receive BNT162b2 or BNT162b2 OMI.
[redacted] SDTM Creation: 11APR2022 (01:32) Source Data: adsl Table Generation: 18MAY2022 (12:24)
(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 08APR2022) Output File: ./nda2_ubd/C4591031_D_PVP/adsl_boost_s932

Table 24. Exposure to BNT162b2 by Race/Ethnic Origin (C4591031 Substudy D) – Cohort 2

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2 OMI	Total Number of Vaccine Doses	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg				
Racial origin				
White	237	237	227	227
Black or African American	21	21	34	34
Asian	42	42	45	45
American Indian or Alaska Native	1	1	4	4
Native Hawaiian or other Pacific Islander	2	2	3	3
Multiracial	10	10	11	11
Not reported	2	2	1	1
Total	315	315	325	325
Ethnic origin				
Hispanic/Latino	48	48	46	46
Non-Hispanic/non-Latino	266	266	279	279
Not reported	1	1	0	0
Total	315	315	325	325

Note: Only subjects ≥18 years of age to ≤55 years of age who have completed 3 doses of BNT162b2 at least 3-6 months prior to randomization were enrolled in study C4591031 Substudy D Cohort 2 to receive BNT162b2 or BNT162b2 OMI.
[redacted] SDTM Creation: 11APR2022 (01:32) Source Data: adsl Table Generation: 18MAY2022 (12:24)
(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 08APR2022) Output File: ./nda2_ubd/C4591031_D_PVP/adsl_boost_s952

Table 25. Exposure to Study Vaccine by Special Population (C4591031 Substudy D) – Cohort 2

Population	Number of Subjects Exposed to BNT162b2 OMI (30 µg) (N^a=315) n^b	Number of Subjects Exposed to BNT162b2 (30 µg) (N^a=325) n^b
Subjects with any baseline comorbidity	159	150
AIDS/HIV	1	0
Any Malignancy + Metastatic Solid Tumor + Leukemia + Lymphoma	2	6
Chronic Pulmonary Disease	37	21
Renal Disease	1	0
Rheumatic Disease	1	2
Mild Liver Disease + Moderate or Severe Liver Disease	1	5
Cerebrovascular Disease + Peripheral Vascular Disease + Myocardial Infarction + Congestive Heart Failure	5	3
Diabetes With/Without Chronic Complication	16	17
Peptic Ulcer Disease	2	0
Obese	135	121

Note: Only subjects ≥18 years of age to ≤55 years of age who have completed 3 doses of BNT162b2 at least 3-6 months prior to randomization were enrolled in study C4591031 Substudy D Cohort 2 to receive BNT162b2 or BNT162b2 OMI.
Note: Comorbidity is based on Charlson Comorbidity Index categories. Subjects identified as belonging to these categories were identified by medical history data collected during the study.
Note: Hemiplegia or Paraplegia only includes preferred terms Hemiplegia and Paraplegia. No participants were identified.

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]).

[redacted] SDTM Creation: 08APR2022 (22:11) Source Data: admh Table Generation: 18MAY2022 (12:24)
(Data Cutoff Date: 11MAR2022, Database Snapshot Date: 08APR2022) Output File: ./nda2_ubd/C4591031_D_PVP/admh_boost_s953

Participants 12 to 17 years of age C4591031 Substudy C

Table 26. Exposure to BNT162b2 by Age Group (C4591031 Substudy C)

Age Group Dose	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
12-17 years		
BNT162b2 (10 µg)		
Booster dose	75	75
BNT162b2 (30 µg)		
Booster dose	65	65

Note: Only participants ≥12 to <18 years of age who have completed a 2-dose primary series of (30-µg doses) at least 5 months (150 days) prior to randomization were enrolled in study C4591031 Substudy C to receive a booster dose of BNT162b2 at either a 10-µg or 30-µg dose level.
[redacted] SDTM Creation: 18OCT2022 (21:51) Source Data: adsl Table Generation: 30JAN2023 (13:31)
(Data Cutoff Date: 14JUL2022, Database Snapshot Date: 17OCT2022) Output File: ./nda2_ubc/C4591031_C_1MPD_PVP/adsl_boost_s912

Table 27. Exposure to BNT162b2 by Age Group and Gender (C4591031 Substudy C)

	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses	
Age Group Dose	Male	Female	Male	Female
12-17 years				
BNT162b2 (10 µg)	38	37	38	37
BNT162b2 (30 µg)	32	33	32	33
Total	70	70	70	70

Note: Only participants ≥12 to <18 years of age who have completed a 2-dose primary series of (30-µg doses) at least 5 months (150 days) prior to randomization were enrolled in study C4591031 Substudy C to receive a booster dose of BNT162b2 at either a 10-µg or 30-µg dose level.
[redacted] SDTM Creation: 18OCT2022 (21:51) Source Data: adsl Table Generation: 30JAN2023 (13:25)
(Data Cutoff Date: 14JUL2022, Database Snapshot Date: 17OCT2022) Output File: ./nda2_ubc/C4591031_C_1MPD_PVP/adsl_boost_s932

Table 28. Exposure to BNT162b2 by Age Group and Race/Ethnic Origin (C4591031 Substudy C)

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
12-17 years		
BNT162b2 (10 µg)		
Racial origin		
White	55	55
Black or African American	11	11
Asian	7	7
Multiracial	1	1
Not reported	1	1
Total	75	75
Ethnic origin		
Hispanic/Latino	15	15
Non-Hispanic/non-Latino	59	59
Not reported	1	1
Total	75	75
BNT162b2 (30 µg)		
Racial origin		
White	50	50
Black or African American	9	9
Asian	5	5
Native Hawaiian or other Pacific Islander	1	1
Total	65	65
Ethnic origin		
Hispanic/Latino	11	11
Non-Hispanic/non-Latino	53	53
Not reported	1	1
Total	65	65

Note: Only participants ≥12 to <18 years of age who have completed a 2-dose primary series of (30-µg doses) at least 5 months (150 days) prior to randomization were enrolled in study C4591031 Substudy C to receive a booster dose of BNT162b2 at either a 10-µg or 30-µg dose level.
[redacted] SDTM Creation: 18OCT2022 (21:51) Source Data: adsl Table Generation: 30JAN2023 (13:26)
(Data Cutoff Date: 14JUL2022, Database Snapshot Date: 17OCT2022) Output File: ./nda2_ubc/C4591031_C_1MPD_PVP/adsl_boost_s952

Table 29. Exposure to BNT162b2 by Special Population (C4591031 Substudy C) Age Group: 12-17

Population	Number of Subjects Exposed to BNT162b2 (10 µg) (N^a=75) n^b	Number of Subjects Exposed to BNT162b2 (30 µg) (N^a=65) n^b
Subjects with any baseline comorbidity	17	21
Chronic Pulmonary Disease	6	12
Mild Liver Disease + Moderate or Severe Liver Disease	1	0
Obese	12	10

Note: Only participants ≥12 to <18 years of age who have completed a 2-dose primary series of (30-µg doses) at least 5 months (150 days) prior to randomization were enrolled in study C4591031 Substudy C to receive a booster dose of BNT162b2 at either a 10-µg or 30-µg dose level.
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: Hemiplegia or Paraplegia only includes preferred terms Hemiplegia and Paraplegia. No participants were identified.
a. N = number of participants in the specified group.
b. n = Number of participants reporting at least 1 occurrence of any comorbidity or obese (BMI ≥30 kg/m2 [≥16 Years of age] or BMI at or above the 95th percentile from the growth chart [12 through 15 years of age]. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html charts/bmiagerev.htm).
[redacted] SDTM Creation: 18OCT2022 (07:22) Source Data: admh Table Generation: 30JAN2023 (13:29)
(Data Cutoff Date: 14JUL2022, Database Snapshot Date: 17OCT2022) Output File: ./nda2 ubc/C4591031 C 1MPD PVP/admh boost s953

Participants aged 12 years and older (Study C4591044 - Cohort 2/Cohort 3)

Table 30. Exposure to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (C4591044) – Cohort 2 and Cohort 3 Combined

Age Group Dose	Number of Subjects Exposed to BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	Total Number of Vaccine Doses
≥12 years		
Vaccine 30 µg	726	726
Vaccine 60 µg	212	212

Note: Participants ≥12 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose approximately 150 to 365 days prior to enroll in this study were included.
[redacted] SDTM Creation: 07DEC2022 (22:00) Source Data: adsl Table Generation: 05JAN2023 (09:49)
(Data cutoff date: Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]) Output File: ./nda2 ub1044/C4591044 1MPD C23 PVP/adsl s912

Table 31. Exposure to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) by Sex (C4591044) – Cohort 2 and Cohort 3 Combined

	Number of Subjects Exposed to BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		Total Number of Vaccine Doses	
Dose Age Group	Male	Female	Male	Female
Vaccine 30 µg				
≥12 years	310	416	310	416
Vaccine 60 µg				
≥18 years	94	118	94	118
Total	404	534	404	534

Note: Participants ≥12 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose approximately 150 to 365 days prior to enroll in this study were included.
[redacted] SDTM Creation: 07DEC2022 (22:00) Source Data: adsl Table Generation: 05JAN2023 (09:49)
(Data cut off date: Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_PVP/adsl_s931

Table 32. Exposure to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) by Age Group and Sex (C4591044) – Cohort 2 and Cohort 3 Combined

	Number of Subjects Exposed to BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		Total Number of Vaccine Doses	
Dose **Age Group**	**Male**	**Female**	**Male**	**Female**
Vaccine 30 µg				
≥12 years to ≤15 years	36	27	36	27
≥16 years to ≤17 years	23	21	23	21
≥18 years to ≤55 years	112	201	112	201
>55 years to ≤64 years	60	87	60	87
≥65 years to ≤74 years	57	67	57	67
≥75 years to ≤84 years	21	12	21	12
≥85 years	1	1	1	1
Total	310	416	310	416
Vaccine 60 µg				
≥18 years to ≤55 years	47	63	47	63

Table 32. Exposure to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) by Age Group and Sex (C4591044) – Cohort 2 and Cohort 3 Combined

	Number of Subjects Exposed to BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		Total Number of Vaccine Doses	
Dose **Age Group**	**Male**	**Female**	**Male**	**Female**
>55 years to ≤64 years	25	36	25	36
≥65 years to ≤74 years	17	17	17	17
≥75 years to ≤84 years	4	2	4	2
≥85 years	1	0	1	0
Total	94	118	94	118

Note: Participants ≥12 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose approximately 150 to 365 days prior to enroll in this study were included.
[redacted] SDTM Creation: 07DEC2022 (22:00) Source Data: adsl Table Generation: 05JAN2023 (09:49)
(Data cutoff date : Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_PVP/adsl_s932b

Table 33. Exposure to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) by Race/Ethnic Origin (C4591044) – Cohort 2 and Cohort 3 Combined

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	Total Number of Vaccine Doses
Vaccine 30 µg		
Racial origin		
White	585	585
Black or African American	83	83
Asian	43	43
American Indian or Alaska Native	3	3
Native Hawaiian or other Pacific Islander	1	1
Multiracial	10	10
Not reported	1	1
Total	726	726
Ethnic origin		
Hispanic/Latino	83	83
Non-Hispanic/non-Latino	637	637
Not reported	6	6
Total	726	726
Vaccine 60 µg		
Racial origin		
White	182	182
Black or African American	19	19
Asian	11	11
Total	212	212
Ethnic origin		
Hispanic/Latino	26	26
Non-Hispanic/non-Latino	182	182
Not reported	4	4
Total	212	212

Note: Participants ≥12 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose approximately 150 to 365 days prior to enroll in this study were included.
[redacted] SDTM Creation: 07DEC2022 (22:00) Source Data: adsl Table Generation: 05JAN2023 (09:50)
(Data cutoff date : Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]) Output File: ./nda2 ub1044/C4591044 1MPD C23 PVP/adsl s952b

Table 34. Exposure to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) by Special Population (C4591044) – Cohort 2 and Cohort 3 Combined Age Group: 12-17

Population	Number of Subjects Exposed to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (30 µg) (N[a]=107) n[b]	Number of Subjects Exposed to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (60 µg) (N[a]=0) n[b]
Subjects with any baseline comorbidity	14	0
Chronic Pulmonary Disease	8	0
Obese	9	0

Note: MedDRA (v25.1) coding dictionary applied.
Note: Participants ≥12 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose approximately 150 to 365 days prior to enroll in this study were included.
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: Hemiplegia or Paraplegia only includes preferred terms Hemiplegia and Paraplegia. No participants were identified.
a. N = number of participants in the specified group.
b. n = Number of participants reporting at least 1 occurrence of any comorbidity or obese (BMI ≥30 kg/m2 [≥16 years of age] or BMI at or above the 95th percentile from the growth chart [12 through 15 years of age]. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm).
[redacted] SDTM Creation: 07DEC2022 (22:00) Source Data: admh Table Generation: 05JAN2023 (12:52)
(Data cutoff date: Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_PVP/admh_s953

Table 35. Exposure to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) by Special Population (C4591044) – Cohort 2 and Cohort 3 Combined Age Group: 18+

Population	Number of Subjects Exposed to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (30 µg) (N[a]=619) n[b]	Number of Subjects Exposed to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (60 µg) (N[a]=212) n[b]
Subjects with any baseline comorbidity	310	104
AIDS/HIV	1	4
Any Malignancy + Metastatic Solid Tumor + Leukemia + Lymphoma	28	13
Chronic Pulmonary Disease	59	20
Renal Disease	5	4
Cerebrovascular Disease + Peripheral Vascular Disease + Myocardial Infarction + Congestive Heart Failure	26	4
Diabetes With/Without Chronic Complication	5	0
Peptic Ulcer Disease	3	2
Obese	246	81

Note: MedDRA (v25.1) coding dictionary applied.
Note: Participants ≥12 years of age at randomization and have received 3 doses of BNT162b2 30 µg, with the third dose approximately 150 to 365 days prior to enroll in this study were included.
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: Hemiplegia or Paraplegia only includes preferred terms Hemiplegia and Paraplegia. No participants were identified.
a. N = number of participants in the specified group.
b. n = Number of participants reporting at least 1 occurrence of any comorbidity or obese (BMI ≥30 kg/m2 [≥16 years of age] or BMI at or above the 95th percentile from the growth chart [12 through 15 years of age]. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm).
[redacted] SDTM Creation: 07DEC2022 (22:00) Source Data: admh Table Generation: 05JAN2023 (12:52)
(Data cutoff date: Cohort 2 [12OCT2022]/Cohort 3 [31OCT2022]) Output File: ./nda2_ub1044/C4591044_1MPD_C23_PVP/admh_s953

Participants aged 6 months to <2 years and ≥ 2 to < 5 years (Study C4591048 – Substudy B, group 2)

Table 36. Exposure to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg by Age Group (C4591048 Subset of Substudy B Group 2)

Age Group Dose	Number of Participants Exposed to Bivalent BNT162b2 (Original/Omi BA.4/BA.5)	Total Number of Vaccine Doses
≥ 6 months to <2 years		
Vaccine 3 µg	24	24
≥ 2 years to <5 years		
Vaccine 3 µg	36	36

Participants at randomization who have received 3 doses (primary series) of BNT162b2 3 µg, with the last dose 60 to 240 days prior to enrollment in this substudy, were included.
[redacted] SDTM Creation: 08DEC2022 (16:31) Source Data: adsl Table Generation: 03FEB2023 (22:02) (Cutoff date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: (CDISC)/C4591048_B_1MPD_Safety_RMP_PVP_FEB2023/adsl_s912

Table 37. Exposure to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg by Age Group, and Gender (C4591048 Subset of Substudy B Group 2)

	Number of Participants Exposed to Bivalent BNT162b2 (Original/Omi BA.4/BA.5)		
Age Group Dose	Male	Female	Total Number of Vaccine Doses
≥ 6 months to <2 years			
Vaccine 3 µg	10	14	24
≥ 2 years to <5 years			
Vaccine 3 µg	20	16	36

Participants at randomization who have received 3 doses (primary series) of BNT162b2 3 µg, with the last dose 60 to 240 days prior to enrollment in this substudy, were included.
[redacted] SDTM Creation: 08DEC2022 (16:31) Source Data: adsl Table Generation: 03FEB2023 (22:02) (Cutoff date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: (CDISC)/C4591048_B_1MPD_Safety_RMP_PVP_FEB2023/adsl_s932

Table 38. Exposure to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg by Age Group, and Race/Ethnic Origin (C4591048 Subset of Substudy B Group 2)

Age Group Dose Race/Ethnic Origin	Number of Participants Exposed to Bivalent BNT162b2 (Original/Omi BA.4/BA.5)	Total Number of Vaccine Doses
Participants ≥6 months to <2 years		
Vaccine 3 µg		
Racial origin		
White	13	13
Black or African American	1	1
Asian	5	5
Multiracial	5	5
Total	24	24
Ethnic origin		
Hispanic/Latino	4	4
Non-Hispanic/non-Latino	20	20
Total	24	24
Participants ≥2 years to <5 years		
Vaccine 3 µg		
Racial origin		
White	22	22
Black or African American	2	2
Asian	4	4
Multiracial	8	8
Total	36	36
Ethnic origin		
Hispanic/Latino	11	11
Non-Hispanic/non-Latino	25	25
Total	36	36

Participants at randomization who have received 3 doses (primary series) of BNT162b2 3 µg, with the last dose 60 to 240 days prior to enrollment in this substudy, were included.
[redacted] SDTM Creation: 08DEC2022 (16:31) Source Data: adsl Table Generation: 03FEB2023 (22:02) (Cutoff date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: (CDISC)/C4591048_B_1MPD_Safety_RMP_PVP_FEB2023/adsl_s942

Table 39. Exposure to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg by Special Population (C4591048 Subset of Substudy B Group 2) – ≥6 Months to <2 Years of Age

Population	Number of Participants Exposed to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) (N^a=24) n^b
Participants with any baseline comorbidity[c]	1
Asthma	1

Participants at randomization who have received 3 doses (primary series) of BNT162b2 3 µg, with the last dose 60 to 240 days prior to enrollment in this substudy, were included.
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).

[redacted] SDTM Creation: 08DEC2022 (16:32) Source Data: admh Table Generation: 03FEB2023 (22:02) (Cutoff date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: (CDISC)/C4591048_B_1MPD_Safety_RMP_PVP_FEB2023/admh_s953_p2

Table 40. Exposure to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg by Special Population (C4591048 Subset of Substudy B Group 2) – ≥2 to <5 Years of Age

Population	Number of Participants Exposed to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) (N[a]=36) n[b]
Participants with any baseline comorbidity[c]	4
Asthma	1
Obese[d]	3
Disabilities	1

Participants at randomization who have received 3 doses (primary series) of BNT162b2 3 µg, with the last dose 60 to 240 days prior to enrollment in this substudy, were included.
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.
[redacted] SDTM Creation: 08DEC2022 (16:32) Source Data: admh Table Generation: 03FEB2023 (22:02) (Cutoff date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: (CDISC)/C4591048 B 1MPD Safety RMP PVP FEB2023/admh s953 p5

Participants aged 5 years to <12 years (Study C4591048 – Substudy D group 2)

Table 41. Exposure to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg (C4591048 Substudy D Group 2)

Dose	Number of Participants Exposed to Bivalent BNT162b2 (Original/Omi BA.4/BA.5)	Total Number of Vaccine Doses
5 years to <12 years		
Vaccine 10 µg	113	113

Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
[redacted] SDTM Creation: 08DEC2022 (18:48) Source Data: adsl Table Generation: 03FEB2023 (23:32) (Cutoff date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: (CDISC)/C4591048 D 1MPD Safety RMP PVP FEB2023/adsl s911 g2p3

Table 42. Exposure to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg by Sex (C4591048 Substudy D Group 2)

	Number of Participants Exposed to Bivalent BNT162b2 (Original/Omi BA.4/BA.5)		Total Number of Vaccine Doses	
Dose	Male	Female	Male	Female
5 years to <12 years				
Vaccine 10 µg	57	56	57	56

Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
[redacted] SDTM Creation: 08DEC2022 (18:48) Source Data: adsl Table Generation: 03FEB2023 (23:33) (Cutoff date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: (CDISC)/C4591048 D 1MPD Safety RMP PVP FEB2023/adsl s911 sex g2p3

Table 43. Exposure to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10µg by Race/Ethnic Origin (C4591048 Substudy D Group 2)

Dose Race/Ethnic Origin	Number of Participants Exposed to Bivalent BNT162b2 (Original/Omi BA.4/BA.5)	Total Number of Vaccine Doses
5 years to <12 years		
Vaccine 10 µg		
Racial origin		
White	66	66
Black or African American	9	9
Asian	13	13
Multiracial	22	22
Not reported	3	3
Total	113	113
Ethnic origin		
Hispanic/Latino	23	23
Non-Hispanic/non-Latino	90	90
Total	113	113

Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
[redacted] SDTM Creation: 08DEC2022 (18:48) Source Data: adsl Table Generation: 03FEB2023 (23:35) (Cutoff date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: (CDISC)/C4591048 D 1MPD Safety RMP PVP FEB2023/adsl s911 race g2p3

Table 44. Exposure to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg by Special Population (C4591048 Substudy D Group 2)

Population	Number of Participants Exposed to Bivalent BNT162b2 (Original/Omi BA.4/BA.5) 10 µg (N[a]=113) n[b]
Participants with any baseline comorbidity[c]	31
Asthma	8
Blood disorders	1
Feeding tube dependent	2
Obese[d]	10
Disabilities	15
Mood Disorders	1
Neurological disorder	1
No CDC Category match	1

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; MMWR = Morbidity and Mortality Weekly Report.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
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.
[redacted] SDTM Creation: 08DEC2022 (18:49) Source Data: admh Table Generation: 03FEB2023 (23:37) (Cutoff date: 25NOV2022, Snapshot Date: 08DEC2022) Output File: (CDISC)/C4591048_D_1MPD_Safety_RMP_PVP_FEB2023/admh_s953_spl_g2p3

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. 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.
- Study C4591001 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 in Study C4591001 were 12 years of age and older; with the 12- to 15-year-old cohort included in the protocol starting from October 2020.
- The participants enrolled in Study C4591007 were 5 to <12 years, 2 to <5 years, and 6 months to <2 years of age.
- The participants enrolled in C4591031 Substudy E and Substudy D were 18 years of age and older.
- The participants enrolled in C4591048 Substudy D were 5 to <12 years and in Substudy B were 2 to <5 years, and 6 months to <2 years of age.

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 was 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 has been 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 45. 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. **bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants >12 years of age** Through the cut-off date of 12 October 2022 (cohort 2) and through 31 October 2022 (cohort 3) there were no CT cases of pregnancy from C4591044. **Booster dose Participants >55 years of age** Through the cut-off date of, 05 April 2022 (Sentinel cohort) and through 16 May 2022 (expanded cohort) there were no CT cases of pregnancy from C4591031 sub study E. **Booster dose Participants ≥18 years to ≤55 years of age** Through the cut-off date of 11 March 2022, there were no CT cases of pregnancy from C4591031 sub study D, cohort 2. *Original (monovalent)* **Participants 6 months to <5 years of age** Not applicable. **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 from Study C4591001. **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. **(3rd dose) Participants 16 years of age and older** 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. **(3rd dose) Participants 12 to 15 years of age** Through the cut-off date of 03 November 2022, there were no cases indicative of exposure during pregnancy originating from Study C4591001 in participants enrolled in the booster group. **(3rd dose) Participants 5 to <12 years of age** Through the cut-off date of 22 March 2022, there were no cases of pregnancy from study C4591007.

Table 45. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
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. **bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants >12 years of age** Through the cut-off date of 12 October 2022 (cohort 2) and through 31 October 2022 (cohort 3) there were no CT cases of breastfeeding from C4591044. **Booster dose Participants >55 years of age** Through the cut-off date of 05 April 2022 (Sentinel cohort) and through 16 May 2022 (expanded cohort) there were no CT cases reporting breastfeeding from C4591031 sub study E. **Booster dose Participants ≥18 years to ≤55 years of age** Through the cut-off date of 11 March 2022, there were no CT cases reporting breastfeeding from C4591031 sub study D, cohort 2. *Original (monovalent)* **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 from Study C4591001. **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 from Study C4591001. **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 6 months to <5 years of age** Not applicable. **(3rd dose) Participants 16 years of age and older** 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. **(3rd dose) Participants 12 to 15 years of age** Through the cut-off date of 03 November 2022, there were no cases indicative of exposure during breast feeding originating from Study C4591001 in participants enrolled in the booster group. **(3rd dose) Participants 5 to <12 years of age** Not applicable.

Table 45. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
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. **bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants >12 years of age** Please refer to the exposure of special populations in Table 34 and Table 35 from study C4591044. **bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants aged 6 months to <2 years and ≥ 2 to < 5 years** Please refer to the exposure of special populations in Table 39 and Table 40 from C4591048 substudy B, group 2. **bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants aged 5 years to <12 years** Please refer to the exposure of special populations in Table 44 from C4591048 Substudy D group 2. **Booster dose Participants >55 years of age** Please refer to the exposure of special populations in Table 21 from C4591031 sub study E. **Booster dose Participants ≥18 years to ≤55 years of age** Please refer to the exposure of special populations in Table 25 from C4591031 sub study D, cohort 2. *Original (monovalent)* **Participants 16 years of age and older** Please refer to the exposure of special populations in Annex 7. **Participants 12 to 15 years of age** Please refer to the exposure of special populations in Annex 7. **Participants 5 to < 12 years of age** Please refer to the exposure of special populations in Annex 7. **Participants 6 months to <5 years of age** Please refer to the exposure of special populations in in Annex 7. **(3rd dose) Participants (16 years of age and older)** Please refer to the exposure of special populations from C4591001 in Annex 7. **(3rd dose) Participants 12 to 15 years of age** Please refer to the exposure of special populations from C4591001 in Annex 7. **(3rd dose) Participants (5 to <12 years of age)** Please refer to the exposure of special populations from C4591007 in Annex 7.

Table 45. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Population with relevant different ethnic origin/race	Please refer to 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 6 months of age have not yet been established. Limited data are available. The safety and efficacy of bivalent BNT162b2 (original/Omi BA.1) in children aged less than 12 years of age has not yet been established. The safety and efficacy of bivalent BNT162b2 (original/Omi BA.4/BA.5) in children aged less than 6 months of age has not yet been established. **bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants aged 6 months to <2 years and ≥ 2 to < 5 years** A total of 60 participants ≥6 months to <5 years of age received a fourth dose with bivalent BNT162b2 (original/Omi BA.4/BA.5) at 3 µg through the cut-off date of 25 November 2022 in the C4591048 Substudy B Group 2. **bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants aged 5 years to <12 years** A total of 113 participants ≥5 years to <12 years of age received a fourth dose with bivalent BNT162b2 (original/Omi BA.4/BA.5) at 10 µg through the cut-off date of 25 November 2022 in the C4591048 Substudy D Group 2. **bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants 12 to 17 years of age** A total of 107 participants received bivalent BNT162b2 (original/Omi BA.4/BA.5) after 3 doses of BNT162b2 30 µg, through the cut-off date of 12 October 2022 in study C4591044. *Original (monovalent)* **Participants 6 months to <5 years of age** As of the cut-off date of 29 April 2022: • 3013 participants in the blinded-placebo controlled follow-up period received the Pfizer-BioNTech COVID-19 vaccine. • 650 participants in the open-label follow-up period after the unblinding in participants who originally received placebo and then received the Pfizer-BioNTech COVID-19 vaccine. Moreover, 76 participants turned 5 years of age, then received Pfizer-BioNTech COVID-19 vaccine at the age-appropriate dose level of 10 µg. • 687 participants in the open-label follow-up period who originally received Pfizer-BioNTech COVID-19 vaccine. Moreover, 121 participants who turned 5 years of age, then received Pfizer-BioNTech COVID-19 vaccine at the age-appropriate dose level of 10 µg. **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 study C4591007 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 in study C4591001. **Participants 16 years of age and older** Six hundred and seventy-one (671) paediatric participants 16 to 17 years of age received COVID19 mRNA vaccine through the DLP of 13 March 2021 in study C4591001.

Table 45. Exposure of Special Populations included or not in Clinical Trial Development Programmes

Type of special population	Exposure
	Booster (3rd dose) Participants 12 to 15 years of age A total of 825 participants in Phase 3 of study C4591001 received a booster (3rd) dose 30 µg of Pfizer-BioNTech COVID-19 Vaccine through the cut-off date of 03 November 2022. **Booster (3rd dose) Participants 5 <12 years of age** A total of 401 participants in Phase 2/3 of study C4591007 received a booster (3rd) dose 10 µg of Pfizer-BioNTech COVID-19 Vaccine through the cut-off date of 22 March 2022; a total of 24 participants, who were 5 to <12 years of age at the time of the study enrollment, turned 12 years of age during the study or after the BNT162b2 10-µg two-dose primary series vaccination period, then received BNT162b2 Dose 3 at the age-appropriate dose level of 30 µg.
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. 4237 participants in the open-label follow-up period after unblinding Nineteen (19) participants 65 years of age and over were from study BNT162-01 study through the cut-off date of 23 October 2020. **bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants 65 years of age and older** Please refer to the exposure Tables from study C4591044. **Booster dose Participants 65 years of age and older** Please refer to the exposure Tables from C4591031 sub study E. *Original (monovalent)* **Booster (Participants 65 years of age and older** 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

MAH and License Partner Data – Cumulative Exposure

MAH Data

The number of doses cumulatively administered (as per public available data for the EEA[6] countries, the US[7], and Japan[8]) is currently updated on a bi-weekly base. Considering the current status of the vaccination schedule and the availability of only partial data published on the ECDC websites for doses of BNT162b2 vaccines (original and bivalent) administered in the EU-EEA countries,[9] it is no longer applicable to estimate the number of doses administered from those shipped. Estimated administered doses were provided separately, as available on the public source data.

Approximately 4,615,732,025[10] doses of BNT162b2 (original and bivalent) were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 18 June 2023. The worldwide estimated cumulative number of shipped doses by vaccine presentation, region and countries and by age group based on data provided in the shipment tracker (Order Book)[11] through 18 June 2023 is showed in Table 46 through Table 48. Out of the cumulative number of shipped doses, 4,154,348,225 were original and bivalent adult presentations (including PBS and Tris/Sucrose); 461,383,800 were original and bivalent paediatric presentations; 686,454,460 were bivalent vaccines of which 21,075,900 were paediatric presentations; 2,446,319,885 doses of BNT162b2 (original and bivalent) were shipped to ROW.

[6] https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea, Accessed on 16 June 2023.

[7] https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-booster-percent-pop5, Last updated on 12 May 2023 and accessed on 14 July 2023.

[8] https://www.kantei.go.jp/jp/headline/kansensho/vaccine html, Accessed on 21 June 2023, 12:00 [JST].

[9] COVID-19 Vaccine Tracker | European Centre for Disease Prevention and Control (europa.eu)

[10] The total includes doses shipped for COVAX, USG Donation and EC Donation programs; does not include CP data.

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

Table 46. Cumulative Estimated Shipped Doses of BNT162b2 Original by Region Worldwide and Age Group

Region/Country	% of Total Doses[a]	6-month – 4 years	5 – 11 years	≥12 years[b]	All
Europe	**30.9**	**4368000**	**69859200**	**1139387235**	**1213614435**
European Union (27)	22.4	3355200	57434400	820816440	881606040
European Economic Area Countries (3)	0.3	9600	452400	12007185	12469185
Switzerland	0.3	0	600000	11397330	11997330
UK	3.3	1003200	10993200	117557895	129554295
Other Countries	3.2	0	57600	126781515	126839115
Commonwealth of Independent States	1.3	0	321600	50826870	51148470
North America	**14.9**	**15379300**	**70749800**	**501181315**	**587310415**
US	13.0	13669300	64199800	433517935	511387035
Canada	1.9	1710000	6550000	67663380	75923380
Central and South America	**15.6**	**24694800**	**86753900**	**502138755**	**613587455**
Asia	**29.9**	**13657200**	**135614200**	**1026803760**	**1176075160**
Japan	7.1	10017600	16016400	252909540	278943540
Other Countries	22.8	3639600	119597800	773894220	897131620
Oceania	**2.2**	**1195200**	**12203400**	**74875230**	**88273830**
Australia/New Zealand	2.2	1195200	12129600	73584360	86909160
Other Countries	0.0	0	73800	1290870	1364670
Africa	**6.4**	**0**	**5832900**	**244583370**	**250416270**
Total	**100**	**59294500**	**381013400**	**3488969665**	**3929277565**

a. The sum of percentages may not exactly match 100% due to rounding in calculations.
b. Including PBS purple cap and Tris/sucrose grey cap.

Table 47. Cumulative Estimated Shipped Doses of BNT162b2 Bivalent Omi BA.1 by Region Worldwide and Age Group

Region/Country	≥12 years	All
Europe	**76181760**	**76181760**
European Union (27)	47076480	47076480
European Economic Area Countries (3)	1016640	1016640
Switzerland	3084480	3084480
UK	25004160	25004160
Other Countries	0	0
Commonwealth of Independent States	0	0
North America	**0**	**0**
US	0	0
Canada	0	0
Central and South America	**10002960**	**10002960**
Asia	**37004670**	**37004670**
Japan	28088190	28088190
Other Countries	8916480	8916480
Oceania	**4700160**	**4700160**
Australia/New Zealand	4700160	4700160
Other Countries	0	0
Africa	**0**	**0**
Total	**127889550**	**127889550**

Table 48. Cumulative Estimated Shipped Doses of BNT162b2 Omi Bivalent BA.4/BA.5 by Region Worldwide and Age Group

Region/Country	% of Total Doses	6-month – 4 years	5 – 11 years	≥12 years	All
Europe	**38.4**	**0**	**1814400**	**212616720**	**214431120**
European Union (27)	34.9	0	1795200	192931920	194727120
European Economic Area Countries (3)	0.5	0	19200	2554560	2573760
Switzerland	0.0	0	0	48960	48960
UK	2.5	0	0	13999680	13999680
Other Countries	0.1	0	0	800640	800640
Commonwealth of Independent States	0.4	0	0	2280960	2280960
North America	**22.4**	**4066600**	**11893700**	**109343620**	**125303920**
US	19.8	4066600	11070100	95708860	110845560
Canada	2.6	0	823600	13634760	14458360
Central and South America	**11.9**	**0**	**114000**	**66293280**	**66407280**
Asia	**23.5**	**0**	**3187200**	**127897470**	**131084670**
Japan	18.0	0	2016000	98662590	100678590
Other Countries	5.4	0	1171200	29234880	30406080
Oceania	**3.4**	**0**	**0**	**18786240**	**18786240**
Australia/New Zealand	3.4	0	0	18766080	18766080
Other Countries	0.0	0	0	20160	20160
Africa	**0.5**	**0**	**0**	**2551680**	**2551680**
Total	**100**	**4066600**	**17009300**	**537489010**	**558564910**

Contractual party (CP) Data

Cumulative CP (Fosun) data on the number of original BNT162b2 and bivalent doses administered in Hong Kong, Macau and Taiwan is provided in Table 49.

Table 49. Cumulative Administered Doses of BNT162b2 Original and BNT162b2 Bivalent Omi BA.4/BA.5 Vaccine – License Partner Data

Region Country -Vaccine Presentation	Number of Administered Doses
Asia	
Hong Kong[a]	
- BNT162b2 (Original)	11428078
- Bivalent (Original + BNT162b2 Omi BA.4/BA.5) 15/15 µg	556625
Macau[b]	397380
Taiwan[c]	
- BNT162b2 (Original)	19887200

a. Cumulatively through 20 June 2023, except for Bivalent data cumulatively through 23 June 2023.
b. For Macau no discrimination between administration data for BNT162b2 Original and BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) was possible.
c. Cumulatively through 13 June 2023.

Cumulative Exposure Data (Health Authority Public Data)

Estimated cumulative data about the number of COMIRNATY® doses administered are published for EEA countries, Japan, and US on the respective Health Authorities' websites.

Table 50 displays the EEA published data with number of doses administered for each age group and by vaccine type.

Data downloaded for the EEA countries should be considered in the following context:

- BNT162b2 original was approved in the 6 months through 4 years age population on 20 October 2022,
- BNT162b2 bivalent Omi BA.1 was approved in 12 years of age and older on 01 September 2022,
- BNT162b2 bivalent Omi BA.4/BA.5 was approved in 12 years of age and older on 12 September 2022, and
- BNT162b2 bivalent Omi BA.4/BA.5 was approved in 5 years through less than 12 years of age on 10 November 2022.

Table 50. EU/EEA – Cumulative Number of BNT162b2 Original and BNT162b2 Bivalent Omi Vaccines Administered Doses by Age Group

Age Group	BNT162b2 Original[a]	BNT162b2 Bivalent Omi BA.1[b]	BNT162b2 Bivalent Omi BA.4/BA.5[c]	BNT162b2 Bivalent Omi[g]	TOTAL
< 18 years	27055225	25854	65085c	25068c	27171232
0 – 4 years	15576[d]	NA[e]	NA[e]	NA[e]	15576
5 – 9 years	4143991[h]	NA[e]	2510[f]	0	4146501
10 – 14 years[f]	4336133	830	9472	7864	4354299
15 – 17 years	8230880	4099	9601	19266	8263846
18 – 24 years	30506062	136044	113494	97169	30852769
25 – 49 years	138812452	1016068	1374517	97169	141300206
50 – 59 years	67561353	1064487	1805745	961536	71393121
60 – 69 years	55528600	1592713	1352473	2687844	61161630
70 – 79 years	54055930	1992782	1155012	2733674	59937398
≥ 80 years	40376375	1283438	1313886	2130269	45103968
Age Unknown	263332	43	160	0	263535
All	**497783992**	**7085524**	**15136438**	**9470237**	**529476191**

a. Cumulative period: from 2020 week 50 through 2023 week 24 (up to 17 June 2023).
b. Cumulative period: from 2022 week 35 through 2023 week 24.
c. Cumulative period: from 2022 week 37 through 2023 week 24.
d. BNT162b2 Original for 6 months through <5 years was approved in EU/EEA on 20 October 2022; correspondent data for BNT162b2 original evaluated from 2022 week 42 through 2023 week 24.
e. Not approved.
f. BNT162b2 Bivalent Omi BA.4/BA.5 for 5 through <12 years was approved in EU/EEA on 10 November 2022; correspondent data for evaluated BNT162b2 Bivalent Omi BA.4/BA.5 from 2022 week 45 through 2023 week 24.
g. Not specified if BA.1 or BA.4/BA.5.
h. Line extension 5-11 years old Tris/Sucrose Paediatrics approved on 03 December 2021 (week 48); cumulative period: from 2021 week 48 through 2023 week 24.

Source: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed on: 18 June 2023. Some data are smaller than those available on 17 December 2022.

Table 51 through Table 54 provide the cumulative total number of administered Comirnaty dose for both original BNT162b2 and bivalent OMI in EU/EEA, per country, and by age group for each dose.

Table 51. EU/EEA – Cumulative Number of Original Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	Unknown
< 18 years	12772444	11783695	2489188	8686	113	0	1099
18 – 24 years	12277974	11419732	6665254	138481	531	0	4090
25 – 49 years	54905456	52439365	30147700	1276743	5979	3	37206
50 – 59 years	25318917	24710183	16274987	1222779	7159	7	27321
60 – 69 years	17376228	17249116	17415639	3439785	16515	53	31264
70 – 79 years	17143899	17012880	15672261	4170325	28685	214	27666
≥80 years	12919083	12708906	10925297	3760840	48832	112	13305
Age Unknown	104661	83133	62067	12890	106	0	475

Table 51. EU/EEA – Cumulative Number of Original Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	Unknown
All	178554954	173436375	125261274	20178211	211936	389	140853

Cumulative period: from 2020 week 50 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

Table 52. EU/EEA – Cumulative Number of Bivalent Omi BA.1 Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
< 18 years	277	444	11888	12899	346	0	0	0
18 – 24 years	344	468	16385	115384	3427	0	0	36
25 – 49 years	1711	1793	69325	906348	36710	3	1	177
50 – 59 years	518	533	30814	983977	48567	10	0	68
60 – 69 years	593	437	39565	1416300	135597	83	0	138
70 – 79 years	583	432	32000	1714923	244339	186	0	319
≥80 years	582	530	20852	599519	661574	108	1	272
Age Unknown	2	3	4	27	3	0	0	4
All	4331	4193	208941	5736450	1130214	390	2	1003

Cumulative period: from 2022 week 35 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

Table 53. EU/EEA – Cumulative Number of Bivalent Omi BA.4/BA.5 Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	Unknown
< 18 years	690	1056	29965	33048	314	12	0
18 – 24 years	1151	1802	37917	133976	2998	31	85
25 – 49 years	4350	5085	154606	1173416	35810	629	621
50 – 59 years	1128	1387	79326	1670423	52231	806	444
60 – 69 years	1228	1040	89603	2196799	193169	3551	870
70 – 79 years	985	913	61027	1734478	334360	41589	522
≥80 years	947	1101	32351	813106	441324	24854	203
Age Unknown	2	2	14	122	14	0	6
All	45417	57883	692205	11125391	3141346	71460	2736

Cumulative period: from 2022 week 37 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

Table 54. EU/EEA – Cumulative Number of Bivalent Omi Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5
< 18 years	17	26	26347	1977	146
18 – 24 years	16	37	43894	52452	770
25 – 49 years	79	162	164716	682991	11797
50 – 59 years	14	31	70073	875905	15513
60 – 69 years	11	23	66471	2599021	22318
70 – 79 years	14	29	37364	2682644	13623
≥80 years	23	31	36474	2087695	6046
Age Unknown	0	0	0	0	0
All	157	313	418992	8980708	70067

Not specified if BA.1 or BA.4/BA.5. Being the Omi variant unknown, the same approach of BA.4/BA.5 has been taken. Cumulative period from 2022 week 37 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

Table 55 through Table 56 show the cumulative number of Original BNT162b2 and Bivalents vaccines doses administered in Japan, respectively. The number of bivalent administered doses alone is not available.

Table 55. Japan - Cumulative Number of Original and Bivalent Omi Administered Doses (1st and 2nd)

Population(s)	Number of Doses	
	1st Dose	**2nd Dose**
General population[a]	81813346	81362856
Elderly[c]	32183220	32108377
Child (5 to < 12 years)	1765076	1710809
Infant only (6 months – 4 years)	174484	161696
Medical workers[b]	6378205	5709228
All	**88191551**	**87072084**

a. Including elderly, children and infants.
b. Counting of vaccinations for medical workers (1st and 2nd dose) ended on 30 July 2021.
c. This reported value is smaller respect the one reported in PSUR #4. Administration data corrected between PSUR #4 and PSUR #5.
Source: Government's website: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html. Accessed on: 21 June 2023, 12:00 [JST].

Table 56. Japan - Cumulative Number of Original and Bivalent Omi Administered Doses (3rd through 6th)

Population(s)	Number of Doses			
	3rd Dose	**4th Dose**	**5th Dose**	**6th Dose**
General population[a]	52736726	42862105	30130339	9129040
Elderly	20758817	20392809	23915646	8285215
Child (5 to < 12 years)	711738	144388	7	N/A
Infant only (6 months – 4 years)	122430	N/A[b]	N/Ab	N/Ab

a. Including elderly, children and infants
b. Booster vaccination for subjects aged 6 months through less than 5 years is not approved in Japan.
Source: https://www kantei.go.jp/jp/headline/kansensho/vaccine.html.
Accessed on: 21 June 2023, 12:00 [JST].

Currently there are no available public data that allow to estimate the COMIRNATY® exposure by gender.

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 57.

Table 57. 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

C4591048 Substudy B Group 2 Subset (≥6 Months to <5 Years of Age: Fourth Dose With bivalent BNT162b2 (original/Omi BA.4/BA.5) at 3 µg

In this initial subset of 60 participants, the frequencies of local and systemic reactions reported within 7 days after administration of bivalent BNT162b2 (original/Omi BA.4/BA.5) at 3 µg were lower than the frequencies previously observed in association with BNT162b2 within the respective age group.

C4591048 Substudy D Group 2 (≥5 to <12 Years of Age): Fourth Dose With bivalent BNT162b2 (original/Omi BA.4/BA.5) at 10 µg

The reactogenicity profile within 7 days after bivalent BNT162b2 (original/Omi BA.4/BA.5) was generally similar to that previously observed in association with BNT162b2 within the respective age group.

C4591044 Cohorts 2 (≥12 Years of Age) and 3 (≥18 Years of Age): Fourth Dose of bivalent BNT162b2 (original/Omi BA.4/BA.5) at 30 or 60 µg

The reactogenicity profile within 7 days after bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine was generally similar to that previously observed in association with booster doses of an omicron BA.1-modified BNT162b2 bivalent vaccine and to BNT162b2 within the respective age groups at the same dose. Both local reactions and systemic events for participants who received the 30-µg dose level tended to be lower for adults >55 years of age compared with younger participants (18 through 55 years of age). There was an observed dose dependency for reactogenicity between the bivalent BNT162b2 (original/Omi BA.4/BA.5) 30- and 60-µg groups with most local reactions and systemic events reported more frequently after a 60-µg dose, which is consistent with prior observations for BA.1-modified bivalent and monovalent vaccines.

C4591031 Substudy E (Expanded Cohort >55 years of age)

Local Reactions

Pain at injection site was the most frequently reported local reaction within 7 days after study vaccination, with swelling and redness at the injection site reported much less frequently. Most local reactions were mild or moderate in severity and all events resolved within a median duration of 1 to 2 days after onset.

Systemic Events

Fatigue was the most frequently reported systemic event reported within 7 days after study vaccination, followed by headache, and less frequently chills, muscle and joint pain. Vomiting, diarrhoea and fever were the least frequently reported systemic events. Most systemic events were mild or moderate in severity and all events resolved within a median duration of 1 to 2 days after onset.

C4591031 Substudy D (18 to 54 years of age)

Local Reactions

Any local reactions reported within 7 days after first study (Dose 4) vaccination for Cohort 2 participants were similar in the BNT162b2 OMI 30 µg (78.6%) and BNT162b2 30 µg (79.4%) groups. Most events were mild or moderate in severity, with the majority arising within the first 1 to 2 days after dosing and were short-lived. No Grade 4 local reactions were reported.

Systemic Events

Any systemic events reported within 7 days after first study (Dose 4) vaccination for Cohort 2 participants were similar in the BNT162b2 OMI 30 µg (77.6%) and BNT162b2 30µg (72.9%) groups, and most events were mild or moderate in severity, with the majority arising within the first 1 to 2 days after dosing and were short-lived. No Grade 4 system events were reported.

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.

Participants 2 to <5 years of age

Local reactions

Pain/tenderness at the injection site was the most frequently reported local reaction within 7 days after each dose, with swelling and redness at the injection site reported much less frequently.

Systemic events

Fatigue was the most frequently reported systemic event reported within 7 days after each dose, at similar frequencies in the BNT162b2 and placebo groups.

Participants 6 Months to <2 Years of Age

Local Reactions

Tenderness at the injection site was the most frequently reported local reaction within 7 days after each dose, with swelling and redness at the injection site reported much less frequently.

Systemic Events

Irritability was the most frequently reported systemic event reported within 7 days after each dose, followed by drowsiness and decreased appetite.

Overall, reactogenicity to three doses of vaccine was mostly mild to moderate and short-lived, with most events occurring at similar or lower frequencies after the third dose compared with the first or second dose of BNT162b2 3-µg in infants and children 6 months to <5 years of age. The median onset of reactogenicity events was typically 1 to 2 days after each dose and most events resolved within 1 to 2 days after onset.

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)[217]

- ACCESS protocol[218]
- US CDC (preliminary list of AESI for VAERS surveillance)[219]
- 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: 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.

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.[220] Additionally 2 clinical studies of the safety and immunogenicity of the COVID-19 vaccine in pregnant women are ongoing (C4591009, and C4591015[12]); 2 non-interventional studies (C4591051 and C4591052) 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 vaccines (including modified vaccines) are planned and another 2 non-interventional studies, C4591021 and C4591022[13] 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.

No data are available yet regarding the use of bivalent BNT162b2 (original/Omi BA.1) (15/15 mcg) and of bivalent BNT162b2 (original/Omi BA.4/BA.5) (15/15 mcg) and of Comirnaty Omicron XBB.1.5 during pregnancy and breast feeding.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following

[12] Study C4591015 is completed with CSR in progress.

[13] Please note that studies C4591009, C4591021 (former ACCESS/VAC4EU) C4591022, C4591051 and C4591052 address only “Use in pregnancy” and not “Breast feeding”.

vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen.

In addition, observational data from women who were breast feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants.

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. Two studies C4591021(non-interventional) and C4591024 (international former Safety and immunogenicity study in high-risk adults)] to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age are ongoing.

The efficacy of bivalent BNT162b2 (original/Omi BA.1) (15/15 mcg) and of bivalent BNT162b2 (original/Omi BA.4/BA.5) (15/15 mcg) may be lower in immunocompromised individuals.

Two additional observational studies (C4591051 and C4591052) to assess the association between COVID-19 bivalent Omicron-modified Vaccine and safety events of interest among also immunocompromised patients are planned.

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: Long term safety data

Risk-benefit impact

The long-term safety of COVID-19 mRNA vaccine is not fully known at present, however further safety data have been collected in Study C4591001 (completed) for up to 2 years following administration of dose 2 of COVID-19 mRNA vaccine and 2 non-interventional studies are ongoing (C4591036 and C4591038).

Two additional planned observational studies (C4591051 and C4591052) will capture safety events in individuals of any age who received the COVID-19 bivalent Omicron-modified vaccine since its availability.

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

- In accordance with CHMP positive opinion (EMEA/H/C/005735/II/0087) received on 10 March 2022 and based on the accumulation of post-authorization safety information, anaphylaxis has been removed as an IIR in the list of safety concerns because anaphylaxis is a known risk of vaccines that is understood by HCPs who administer vaccines and patients and does not considerably impact the benefit/risk profile of the vaccine. Product labeling and standards of medical care during the vaccination procedure provide adequate risk mitigation.

- In accordance with the preliminary PSUR assessment report (EMEA/H/C/PSUSA/00010898/202212) received on 12 May 2023, the important potential risk VAED/VAERD is removed from the list of safety concerns of the RMP, as the available cumulative data (clinical trial and post-marketing data) showed no safety information that substantiates retaining VAED/VAERD as an important potential risk. VAED/VAERD will continue to be monitored through routine pharmacovigilance.

- The MAH removes the missing information "Interaction with other vaccines" on the basis of the C4591030 final study report and the non-interventional effectiveness data from a large retrospective cohort study of commercially insured US adults conducted by Pfizer supported by the results from 15 prospective study publications describing the effect of coadministration of COVID-19 vaccine dose(s) with an influenza vaccine on immune responses and safety. In summary, the available clinical data from the COVID-19 vaccine program, published literature, and real-world data collectively support the safety, immunogenicity, and effectiveness of coadministration of COVID-19 vaccine with SIVs and allow it to be removed from the list of safety concerns as missing information. The MAH will add data on co-administration with influenza vaccine to the product information via a Type 2 variation and will continue monitoring interactions with this and other vaccines through routine surveillance.

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: Myocarditis and Pericarditis

Table 58. 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. **Participants 5 to < 12 years of age** The MMWR[221] issued on 01 April 2022, estimated the incidence of myocarditis and pericarditis after infection, MIS and vaccination using EHR data from 40 US health care systems participating in PCORnet, the National Patient-Centered Clinical Research Network (7) for the period January 1, 2021–January 31, 2022. In this study, 27% of persons received mRNA-1273 (Moderna) vaccine and 73% received BNT162b2 (Pfizer-BioNTech) vaccine. In the unspecified dose cohort, 36% received Moderna and 64% Pfizer-BioNTech. In the any dose cohort, 29% received Moderna and 71% Pfizer-BioNTech. Doses specified as booster doses were excluded. Among males aged 5–11 years, the incidences of myocarditis and myocarditis or pericarditis using a 7 and 21-day window were 0–4 after the first vaccine dose, 0 after the second dose, and 12.6–17.6 cases per 100,000 after infection. Among females aged 5-11 years, there were no cases of myocarditis or pericarditis after vaccination; incidences of myocarditis and myocarditis or pericarditis were 5.4–10.8 cases per 100,000 after infection. Because there were no or few cases of myocarditis or pericarditis after vaccination, the RRs for several comparisons could not be calculated or were not statistically significant. The US Centers for Disease Control and Prevention (CDC) presented data at a VRBPAC meeting on 14 June 2022 on the number of myocarditis cases within 7 days and 8-21 days of vaccination per million doses from spontaneous reports through 26 May 2022 in the Vaccine Adverse Event Reporting System (VAERS)[222]. In children 5-17 years of age, 54.8 million Pfizer-BioNTech doses were administered (including 3.8 million booster [third] doses). In general, the reporting rates were higher 0-7 days after vaccination than after 8-21 days across age groups and sexes. In the 0-7-day risk interval post dose 2, the crude reporting rates were highest in ages 16-17 years followed by 12-15 years and lowest for 5-11 years. For persons 5-11 years of age, the reporting rates in the 0-7-day risk interval were (per 1 million doses administered): 0.2 post dose 1, 2.6 post dose 2, and 0 post booster in males; 0.2 post dose 1, 0.7 post dose 2, and 0 post booster in females. The reporting rates were slightly elevated post dose 2 in males, compared with the estimated background rates (0.2-2.2 per 1-million-person days in the 0–7-day interval). No excess cases were numerically estimated by authors in this analysis. Data from the Vaccine Safety Datalink (VSD) active surveillance network shared publicly by the CDC on 14 June 2022 showed the incidence rates of chart confirmed myocarditis or pericarditis treated in emergency department or inpatient settings within 0-7 days post mRNA COVID-19 primary series and booster through 28 May 2022. The occurrence of myocarditis and pericarditis was rare (n=3 post dose 2) based on approximately 800,000 doses administered in children 5-11 years of age, and lowest of the other reported age groups (12-15 and 16-17 years). The reported incidence rates per million doses administered 0-7 days post vaccination had wide reported confidence intervals (males, 15.2 [95% CI 3.1-44.5]; females, 0 [95% CI 0-15.6]), suggesting instability and low precision. Hause et al provided an analysis of safety of BNT162b2 vaccination among US children 5-11 years of age using 3 vaccine safety monitoring systems: v-safe (a voluntary smartphone-based system that monitors reactions and health effects), VAERS (the national spontaneous reporting system co-managed by CDC and Food and Drug Administration [FDA]), and VSD (an active surveillance system that monitors electronic health records for prespecified events, including myocarditis). [223] The estimated exposure in this age group at the date of the report was >16 million vaccine doses. In VAERS, the reporting rate of verified myocarditis during days 0–7 after dose 2 was substantially lower among males ages 5–11 years (2.2 per 1 million doses administered) than males ages 12–15 years (45.7 per 1 million doses administered). In weekly sequential analyses of VSD data, no signal for an increased risk of myocarditis after vaccination was found.

Table 58. Myocarditis and Pericarditis[a]

Participants 12 to 15 years of age
As per MMWR[221] (01 April 2022), among males aged 12–17 years, the incidences of myocarditis and myocarditis or pericarditis were 2.2–3.3 after the first vaccine dose, 22.0–35.9 after the second dose, and 50.1–64.9 cases per 100,000 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 4.9–69.0, and with second dose recipients, were 1.8–5.6; all RRs were statistically significant. Among females aged 12-17 years, incidences of myocarditis or pericarditis were 2.0 after the first vaccine dose, 2.1-5.4 after the second vaccine dose, and 24.7-35.7 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 25.7-19.8, and with second dose recipients, were 2.5-2.2; all RRs were statistically significant.

In a prospective nationwide multicenter study from Denmark[224] among individuals 12–17 years of age, the study revealed an incidence of 97 males and 16 females with myocarditis following COVID-19 vaccination per million. During the first 12 months of the COVID-19 era, the incidence of MIS-C and elevated troponin was 355 and 187 per million male and female adolescents (12-17 years) infected with SARS-CoV-2 (1 in 2800 males and 1 in 5300 females), significantly higher than the incidence of myopericarditis after COVID-19 vaccination in both males and females (Fisher's exact test; $P < 0.01$). In another Danish population-based cohort study[225], vaccination with BNT162b2 was associated with a significantly increased rate of myocarditis or myopericarditis among women only - in the 12-39 years age group, the absolute rate was 1.6 (95% CI 1.0 - 2.6) per 100 000 female individuals aged 12-39 years within 28 days of vaccination. In the overall BNT162b2 cohort, the absolute rate was 1.4 (1.0-1.8) per 100,000 vaccinated individuals within 28 days, and among individuals aged 12-17 years, the rate was 1.0 (0.2 to 3.0) per 100 000 individuals within 28 days of BNT162b2 vaccination. In this study, clinical outcomes of myocarditis or myopericarditis were predominantly mild and generally similar between vaccinated and unvaccinated individuals, although precision in describing clinical outcomes was limited owing to few events.

In evaluation of 404,407 adolescents vaccinated with BNT162b2 in Israel, Mevorach et al[226] estimated the risk of myocarditis among male recipients in the 21 days after the first and second doses of 0.56 cases per 100,000 after the first dose and 8.09 cases per 100,000 after the second dose; the risk estimates among female recipients were 0 cases per 100,000 after the first dose and 0.69 cases per 100,000 after the second dose. The risk of myocarditis after receipt of the second vaccine dose among male adolescents 12 to 15 years of age was estimated to be 1 case per 12,361; the corresponding risk among female adolescents was estimated to be 1 case per 144,439. In this study, all the cases were clinically mild, involving a mean duration of hospitalization of 3.1 days (range, 1 to 6) and no readmissions during 30 days of follow-up.

Booster Dose (Participants 12 to 15 years of age)
The most recent estimates for myocarditis and pericarditis following booster dose administration and with inclusion of paediatric age groups were presented publicly by the US CDC on 7 June 2022 and 14 June 2022 at VRBPAC meetings and concerned data from VAERS and VSD. [222]
The VAERS analyses concerned data as of 26 May 2022 and included an estimated 93.4 million booster (third) doses of mRNA vaccines in people 18 years of age or older, and 3.8 million booster (third) doses of BNT162b2 in children 12-17 years of age. The reporting rates of myocarditis at 0-7 days were 15.3, 24.1, 9.9, and 4.8 per million booster doses in males 12-15, 16-17, 18-24, and 25-29 years of age, respectively, with rates being lower than those reported post dose 2 in the same age groups and risk period (46.4, 75.9, 38.9, and 15.2, respectively). The reporting rates of myocarditis 0-7 days post-booster dose did not exceed estimated background incidence for the period in males 30 years of age or older, and in females of any age presented.

The analysis of US VSD[222] reported the incidence rates of chart confirmed myocarditis or pericarditis treated in emergency department or inpatient settings within 0-7 days post mRNA COVID-19 primary series and booster through 28 May 2022 for paediatric age groups. The exposure (ie, doses administered) in the VSD dataset was substantially lower than the overall national exposure utilized for the VAERS estimates above (ie, for children 12-17 years of age, there were 249,775 booster doses in VSD compared to 3.8 million

Table 58. Myocarditis and Pericarditis[a]

booster doses in VAERS estimates). The number of verified myocarditis and/or pericarditis events in the 0–7-day risk interval following boosters in 12-17 years was <10 in males or females, rendering wide reported confidence intervals and therefore a degree of uncertainty in the reported incidences; the data will be surveilled as it accumulates and is disclosed publicly.

In a 20 April 2022[227] presentation of VDS data through 12 April 2022 of people 12-39 years of age, the incidence rates of chart confirmed myocarditis or pericarditis treated in emergency department or inpatient settings within 0-7 days post mRNA COVID-19 primary series and booster were compared to 22 to 42 days after the corresponding vaccine exposure. Myocarditis rates were approximately halved following the booster (third) dose of mRNA COVID-19 vaccine than those following the primary series (with overlapping confidence intervals) for ages 12-39 years: 41.4 per million doses (33.1- 51.1) after BNT162b2 primary series vs 21.4 per million dose (12.7- 33.8) after BNT162b2 booster.

Similarly, in the US publication by Kuehn et al, myocarditis occurrence after booster doses administered to adolescents was estimated by analysing VAERS system and v-safe reports received between 09 December 2021 and 20 February 2022.[228] During the study period, roughly 2.8 million US adolescents received a BNT162b2 booster dose. The confirmed myocarditis rate after a booster dose was 11.4 per 1 million administered doses among adolescent boys 12-17 years of age. By comparison, the myocarditis rate after the second dose in the primary vaccine series was 70.7 per 1 million among individuals 12-15 years of age and 105.9 per 1 million doses among individuals 16-17 years of age.

Participants 16 years of age and older
As per MMWR[221] (01 April 2022), among males aged 18-29 years, the incidences of myocarditis and myocarditis or pericarditis were 2.7-8.1 after the first vaccine dose, 12.1-15.0 after the second dose, and 85.5-100.6 cases per 100,000 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 31.8-12.5, and with second dose recipients, were 7.0-6.7; all RRs were statistically significant. Among males aged 30 years or older, the incidences of myocarditis and myocarditis or pericarditis were 3.8-7.3 after the first vaccine dose, 3.1-7.3 after the second dose, and 100.2-114.0 cases per 100,000 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 26.6-15.6, and with second dose recipients, were 32.3-15.6. Among females aged 18-29 years, incidences of myocarditis or pericarditis were 2.5-4.6 after the first vaccine dose, 3.1-5.2 after the second vaccine dose, and 23.8-33.6 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 9.4-7.4, and with second dose recipients, were 7.6-6.4. Among females aged 30 years or older, incidences of myocarditis or pericarditis were 3.1-6.2 after the first vaccine dose, 1.7-4.1 after the second vaccine dose, and 53.8-61.7 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 17.1-10.0, and with second dose recipients, were 31.2-14.9. The estimates in this study are similar to previous reports by CDC.

An HCO study from Israel[229] found a RR for myocarditis after vaccination of 3.24 (95% CI, 1.55 -12.44; RD 2.7 events per 100,000 persons [95% CI 1.0 to 4.6]) compared with unvaccinated group. The study did not provide age and gender specific stratifications, but it reports that in the vaccinated group with myocarditis, the median age was 25 years (interquartile range, 20 to 34), and 90.9% were male. The same study found an excess risk of myocarditis of 11 events per 100,000 persons after SARS-COV-2 infection. Two further studies from Israel reported similar results. Witberg et al.[230] observed a small excess in events 3–5 days following the second dose of BNT162b2 vaccine, but most were mild presentations and just one classified as fulminant. Mevorach et al.[226] observed an incidence ratio of 5.34 for myocarditis in 5,442,696 persons following BNT162b2, although this was attenuated when restricted to the definite and probable cases of myocarditis. Risk of myocarditis was restricted to males under the age of 40 years and only observed following the second dose.

In a self-controlled case series study of over 38 million people aged 16 or older vaccinated for COVID-19 in England between 1 December 2020 and 24 August 2021[231], authors estimated an extra one (95% CI 0, 2) myocarditis event per 1 million people vaccinated with BNT162b2 in the 28 days following a first dose and with an extra 40 (95% CI 38, 41) myocarditis events per 1 million patients in the 28 days following a SARS-

Table 58. Myocarditis and Pericarditis[a]

CoV-2 positive test. The association with the second dose was not significant for BNT162b2 (IRR 1.3 [95% CI 0.98-1.72]). The risk was higher in participants aged under 40 years, with an estimated 2 (95% CI 1, 3) and 3 (95% CI 2, 4) excess cases of myocarditis per 1 million people receiving a first or second dose of BNT162b2; and 10 (95% CI 7, 11) extra cases of myocarditis following a SARS-CoV-2 positive test in the same age group.

Booster Dose (Participants 16 years of age and older)
Using US VAERS data of adults aged ≥18 years who have met the myocarditis case definition following administration of 81.2 million COVID-19 mRNA booster doses in the United States between 22 September 2021 through 6 February 2022, the US CDC found the rate of myocarditis following BNT162b2 to be highest in males aged 18-24 years (4.1 per 1 million booster doses). The rates for other age groups and females were low (or null).[223]

Two studies from Israel report incidence of myocarditis and pericarditis after booster dose. Aviram et al [232] report that 11,905 recipients >18 years who have received a booster dose throughout August 2021, there were 4 cases of myocarditis: all male and young (21-38 years).
Three out of 4 patients presented a notable medical history, of which 1 had prior myocarditis episodes (2014-2015 presumably associated with a viral infection), and one patient had a history of childhood long QT and genetic mutation in keratin 16 gene; the clinical course was uneventful in all 4 patients. The second study evaluated military personnel in Israel[233] vaccinated with a third dose of BNT162b2 until September 30, 2021, and diagnosed with myocarditis up to October 14, 2021, found the incidence rates of myocarditis in the week and 2 weeks following a third vaccine dose were 3.17 (95% CI, 0.64-6.28) and 5.55 (95% CI, 1.44-9.67) per 100 000 vaccines given, respectively. Because all myocarditis cases were in young men (18-24 years old), authors estimated the incidence for this specific population to be 6.43 (95% CI, 0.13-12.73) and 11.25 (95% CI, 2.92-19.59) per 100,000 vaccines given in the week and 2 weeks after a third vaccine dose, respectively.

Characterisation of the risk

XBB 1.5 administration

Data from the safety database (non-CT) cumulative as of 15 November 2023

Individuals 6 month to <5 years of age
Of a total of 136 reported cases in this age group, there were no cases of myocarditis or pericarditis.

Individuals 5 to 11 years of age
Of a total of 94 reported cases in this age group, there were no cases of myocarditis or pericarditis.

Individuals 12 years of age and older
Of a total of 3,343 reported cases in this age group, there were 18 cases (0.5%) reporting myocarditis (14) or pericarditis (6), all serious. In 2 of these 18 cases, the participant developed both myocarditis and pericarditis.

PT	No. of Events	Events with Criterion of Hospitalization	Fatal	Resolved / Resolving	Not Resolved	Unknown
All PTs	20	6	0	6	4	10
Myocarditis	14	4	0	4	2	8
Pericarditis	6	2	0	2	2	2

bivalent BNT162b2 (original/Omi BA.1 and BA.4/BA.5) administration

Data from the safety database (non-CT) cumulative as of 15 November 2023

Individuals 6 month to <5 years of age
Of a total of 276 reported cases in this age group, there were no cases of myocarditis or pericarditis.

Table 58. Myocarditis and Pericarditis[a]

Individuals 5 to 11 years of age
Of a total of 880 reported cases in this age group, there were no cases of myocarditis or pericarditis.

Individuals 12 years of age and older
Of a total of 28,206 reported cases in this age group, there were 228 cases (0.8%) reporting myocarditis/myopericarditis (152) or pericarditis/pleuropericarditis (106), all serious. In 30 of these 228 cases, the participant developed both myocarditis and pericarditis.

Myocarditis

PT	No. of Events	Events with Criterion of Hospitalization	Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown
All PT-events	156	78	12	54	5	44	41
Eosinophilic myocarditis	2	1	0	1	0	0	1
Giant cell myocarditis	1	1	0	0	0	0	1
Immune-mediated myocarditis	1	1	0	1	0	0	0
Myocarditis	127	57	11	38	4	39	35
Myopericarditis	25	18	1	14	1	5	4

Pericarditis

PT	No. of Events	Events with Criterion of Hospitalization	Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown
All PT-events	106	48	3	44	4	28	27
Pericarditis	104	46	3	43	4	27	27
Pleuropericarditis	2	2	0	1	0	1	0

Original (Monovalent) Administration

Data from the safety database (non-CT) cumulative as of 15 November 2023

Individuals 6 month to <5 years of age
Of a total of 1,263 reported cases in this age group, there were 3 cases (0.2%) reporting myocarditis (1) or pericarditis events (2), all serious.

PT	No. of Events	Events with Criterion of Hospitalization	Not Resolved
All PT-events	3	1	3
Pericarditis	2	0	2
Myocarditis	1	1	1

Individuals 5 to 11 years of age
Of a total of 16,918 reported cases in this age group, there were 125 cases (0.7%) reporting myocarditis/myopericarditis (88) or pericarditis events (46), all serious. In 9 of these 125 cases, the participant developed both myocarditis and pericarditis.

Table 58. Myocarditis and Pericarditis[a]

Myocarditis

PT	No. of Events	Events with Criterion of Hospitalization	Fatal	Resolved / Resolving	Not Resolved	Unknown
All PT-events	90	32	3	48	14	25
Carditis	3	0	0	1	1	1
Myocarditis	65	25	3	34	5	23
Myopericarditis	22	7	0	13	8	1

Pericarditis

PT	No. of Events	Events with Criterion of Hospitalization	Fatal	Resolved / Resolving	Not Resolved	Unknown
Pericarditis	46	7	0	23	10	13

Individuals 12 years of age and older

Of a total of 1,663,467 reported cases in this age group, there were 22,515 cases (1.4%) reporting myocarditis/myopericarditis (13,654) or pericarditis/pleuropericarditis events (10,920), all serious. In 2,059 of these 22,515 cases, the participant developed both myocarditis and pericarditis events.

Myocarditis

PT	No. of Events	Events with Criterion of Hospitalization	Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown
All PT-events	13,811	7,045	250	5,442	431	4,033	3,655
Autoimmune myocarditis	7	5		2	0	1	4
Carditis	173	36	2	33	1	59	79
Chronic myocarditis	5	2	1	0	1	2	1
Eosinophilic myocarditis	17	12	5	9	1	1	1
Giant cell myocarditis	6	6		3	0	1	2
Hypersensitivity myocarditis	7	5	1	5	0	1	
Immune-mediated myocarditis	5	1	1	1	0		3
Myocarditis	11,460	5,441	228	4,363	376	3,342	3,161
Myopericarditis	2,119	1,537	12	1,026	52	626	404

Pericarditis

PT	No. of Events	# Events with Criterion of Hospitalization	Fatal	Resolved /Resolving	Resolved with Sequelae	Not Resolved	Unknown
All PTs	10,956	3,051	47	4,131	206	3,838	2,734

Table 58. Myocarditis and Pericarditis[a]

Autoimmune pericarditis	1	0	0	0	0	1	0
Pericarditis	10,834	2,983	47	4,070	203	3,815	2,711
Pericarditis adhesive	1	0	0	0	0	1	0
Pericarditis constrictive	27	15	0	13	2	6	6
Pleuropericarditis	81	53	0	48	1	15	17

bivalent BNT162b2 (original/Omi BA.4/BA.5) administration

- *Participants 6 month to <5 years of age*

Data from the CT dataset C4591048 Substudy B
Myocarditis and Pericarditis were not observed in any participant through the cut-off date of 25 November 2022.

- *Participants 5 to 11 years of age*

Data from the CT dataset C4591048 Substudy D
Myocarditis and Pericarditis were not observed in any participant through the cut-off date of 25 November 2022.

- *Participants 12 years of age and older*

Data from the CT dataset C4591044 Myocarditis and Pericarditis were not observed in any vaccine group through the cut-off date of 12 October 2022 (cohort 2) and 31 October 2022 (cohort 3).

Original (Monovalent) + bivalent BNT162b2 (original/Omi BA.1)

- *Booster Dose Participants >55 years of age*

Data from the CT dataset C4591031 Substudy E
Myocarditis and Pericarditis were not observed in any vaccine group through the cut-off date of 05 April 2022 (Sentinel cohort) and through 16 May 2022 (Expanded cohort).

- *Booster Dose Participants ≥18 years to ≤55 years of age*

Data from the CT dataset C4591031 Substudy D, cohort 2
Myocarditis and Pericarditis were not observed in any vaccine group through the cut-off date of 11 March 2022.

Original (Monovalent) Administration

- *Participants 6 month to <5 years of age*

Data from the CT dataset (study C4591007)
Through 29 April 2022, there were no cases of myocarditis/pericarditis in this age group.

- *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.In the 6-month post dose 3 data with cut off 23 February 2023, myocarditis and pericarditis were not observed.

- *(3rd) Dose Participants 5 to <12 years of age*

Data from the CT database (study C4591007)
Through 22 March 2022, no cases were retrieved reporting myocarditis and pericarditis in the participants who received a booster dose.

- *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.

- *(3rd) Dose Participants 12 to 15 years of age*

Data from the CT database (Study C4591001)
Through 03 November 2022, no cases were retrieved reporting myocarditis and pericarditis in the participants who received a booster dose.

- *Participants 16 years of age and older*

Data from the CT dataset (Study C4591001)
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:

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.

- *(3rd) 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.

Conclusion: the product labels 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 EU and US CDC has found reports to be most frequent in adolescent and young adult male patients following the second dose of vaccine. The disease course is self-limiting in a vast majority of cases: 95% of patients show a rapid resolution of symptoms and normalization of cardiac biomarkers, electro- and echocardiographic findings within days.[234] Cardiac arrhythmias, cardiac arrest or death were not found significantly associated with the vaccine.[229,235] Importantly, the available data suggest that the incidence rate of myocarditis in the context of COVID-19 is much greater than the risk of myocarditis following vaccination.
Preventability
Healthcare professional should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.
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; Immune-mediated pericarditis.

Individuals 6 month to <5 years of age: includes cases where age in years was provided or where age was not provided, and age group was equal to infant.
Individuals 5 to 11 years of age: includes cases where age in years was provided or where age was not provided, and age group was equal to child.
Individuals 12 years of age and older: includes cases where age in years was provided or where age was not provided, and age group was equal to adolescent, adult and elderly.

Note: BC criteria is no longer applied; please refer to vaccine specific summary safety reports and periodic aggregate reports for further information on the characteristics of the post-marketing cases.

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

c. Includes cases where age in years was provided or where age was not provided, and age group was equal to child.

SVII.3.1.2. Important Potential Risk:

There are no important potential risks.

SVII.3.2. Presentation of the Missing Information

Table 59. 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 60. 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 61. 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 62. 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 63. 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. 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 have been collected from participants in study C4591001 for up to 2 years following the 2nd dose of vaccine. Additionally, active surveillance studies are planned or ongoing to follow long-term safety in vaccine recipients for 2 years following Dose 2.

Module SVIII. Summary of the Safety Concerns

Table 64. Summary of Safety Concerns

Important Identified Risks	Myocarditis and Pericarditis
Important Potential Risks	None
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
	Long term safety data

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

III.1. Routine Pharmacovigilance Activities

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 for signal detection occur on a regular basis and include:

- Receipt and review of individual AE reports (e.g., ADRs);
- Review of aggregated AE reports;
- Use of Data Capture Aids to facilitate the capture of clinical details about various AESIs including:
    - 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.
- Reference to 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;*
- Observed versus expected analyses as appropriate;
- Regulatory authority safety alerts monitoring.

Summary safety reports

The submission of summary safety reports has complemented the submission of 6 monthly PSURs since authorisation. The need and frequency of such reports have been re-evaluated based on the available evidence from post-marketing experience and since 15 April 2022 (DLP of the last report) SSRs are no longer required by EMA as per the final PRAC Assessment Report for PAM-MEA-002.13 - 3. SBSR/14. SSR (report: EMA/PRAC/577594/2022) dated 08 June 2022.

Potential Medication Errors

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

Potential medication errors are mitigated through the information in the SmPC and available resources and referenced materials for healthcare providers and individuals receiving vaccination.

- The EU SmPC (section 6.6) contains instructions for vaccine dilution and administration, vaccination dosing, and storage conditions for the formulations of the COVID-19 mRNA vaccine.

- Dosing card which provides information for vaccine storage, vial differentiation, dose planning, and administration is available, for healthcare provider reference.

- Patient 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.

Vial Differentiation

All vials have specific colour flip off plastic cap and label differentiation factors:

Potential medication errors are mitigated through the information in the label (colour of label boarder, product name on the label) and available resources and referenced materials for healthcare providers.

For PBS sucrose 30 mcg presentation there are neither further plans to re-manufacture nor remaining inventory for sale. The elimination of this presentation may assist with mitigation of medication errors by having fewer available formulations; the formulation is removed from the RMP section.

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

Table 65. Vaccine Presentation Characteristics - 12 years and older

INN	Tozinameran	Tozinameran/ Riltozinameran	Tozinameran/ Famtozinameran	
Name	Comirnaty 30 mcg/dose DO NOT DILUTE Grey Cap	Comirnaty Original/Omicron BA.1 DO NOT DILUTE Grey Cap	Comirnaty Original/Omicron BA.4-5 DO NOT DILUTE Grey Cap	Comirnaty Original/Omicron BA.4-5 DO NOT DILUTE Light Grey Cap
Dose	30 mcg (no dilution)	15/15 mcg (no dilution)	15/15 mcg (no dilution)	15/15 mcg (no dilution)
Vial cap color and Label with Color Border	Grey	Grey	Grey	Light Grey
Dose Volume	0.3 mL	0.3 mL	0.3 mL	0.3 mL
Amount of Diluent Needed per Vial	NO DILUTION	NO DILUTION	NO DILUTION	NO DILUTION
Fill Volume	2.25 mL	2.25 mL	2.25 mL	0.48 mL
Doses per vial	6 doses per vial	6 doses per vial	6 doses per vial	1 dose per vial
Formulation	Tris sucrose	Tris sucrose	Tris sucrose	Tris sucrose
Grey Caps	**Multi dose:** If an attempt is made to dilute the 30 mcg/dose dispersion for injection vial, the user would immediately feel resistance to the addition of any further volume, because the vial fill volume is 2.25 mL and there is little remaining physical space to add diluent to the vial. **Single dose**: The filled volume for this light grey cap vial is only 0.48 mL because it contains 1 dose for extraction. If diluted with sodium chloride 9 mg/mL (0.9%) solution by mistake, more than 1 dose of over diluted vaccine may be erroneously extracted.			

Vaccine Presentation Characteristics - 12 years and older - cont.			
INN	**Raxtozinameran**		
Name	Comirnaty Omicron XBB.1.5 DO NOT DILUTE Grey Cap	Comirnaty Omicron XBB.1.5 DO NOT DILUTE Grey Cap	Comirnaty Omicron XBB.1.5 PFS (Frozen, Plastic) DO NOT DILUTE
Dose	30 mcg (no dilution)	30 mcg (no dilution)	30 mcg (no dilution)
Vial cap color and Label with Color Border	Grey	Light Grey	No cap color Color border - Gold
Dose Volume	0.3 mL	0.3 mL	0.3 mL
Amount of Diluent Needed per Vial/Syringe	NO DILUTION	NO DILUTION	NO DILUTION
Fill Volume	2.25 mL	0.48 mL	0.432 mL
Doses per vial/syringe	6 doses per vial	1 dose per vial	1 dose per syringe
Formulation	Tris sucrose	Tris sucrose	Tris sucrose
Single dose plastic pre-filled syringe: The filled volume for the Frozen, Plastic PFS is only 0.432 mL, because it contains 1 dose for IM administration. Note: Bright Pink differentiator on label of the carton.			

Table 66. Vaccine Presentation Characteristics - 5 through 11 years

INN	**Tozinameran**	**Tozinameran/ Famtozinameran**			**Raxtozinameran**		
Name	Comirnaty 10 mcg/dose DILUTE BEFORE USE Orange cap	Comirnaty Original/Omicron BA.4-5 DILUTE BEFORE USE Orange cap	Comirnaty Original/Omicron BA.4-5 DO NOT DILUTE Dark Blue cap	Comirnaty Original/Omicron BA.4-5 DO NOT DILUTE Light Blue cap	Comirnaty Omicron XBB.1.5 DILUTE BEFORE USE Orange cap	Comirnaty Omicron XBB.1.5 DO NOT DILUTE Blue Cap	Comirnaty Omicron XBB.1.5 DO NOT DILUTE Light Blue Cap
Dose	10 mcg (with dilution)	5/5 mcg (with dilution)	5/5 mcg (no dilution)	5/5 mcg (no dilution)	10 mcg (with dilution)	10 mcg (no dilution)	10 mcg (no dilution)
Vial cap color and Label with Color Border	Orange	Orange	Dark Blue	Light Blue	Orange	Blue	Light Blue
Dose Volume	0.2 mL	0.2 mL	0.3 mL	0.3 mL	0.2 mL	0.3 mL	0.3 mL
Amount of Diluent Needed per Vial	1.3 mL	1.3 mL	NO DILUTION	NO DILUTION	1.3 mL	NO DILUTION	NO DILUTION
Fill Volume	1.3 mL	1.3 mL	2.25 mL	0.48 mL	1.3 mL	2.25 mL	0.48 mL
Doses per vial	10 doses per vial (after dilution)	10 doses per vial (after dilution)	6 doses per vial	1 dose per vial	10 doses per vial (after dilution)	6 doses per vial	1 dose per vial
Formulation	Tris sucrose	Tris sucrose	Tris sucrose	Tris sucrose	Tris sucrose	Tris sucrose	Tris sucrose
Orange caps	If the contents of the vial are not diluted with the required 1.3 mL sodium chloride 9 mg/mL (0.9%) solution, the user would only be able to extract approximately 5 doses instead of 10 doses because the vial fill volume is 1.3 mL. If excess diluent such as 2.2 mL which is the dilution volume for the 3 mcg/dose diluted product (maroon cap amount), is used to dilute the 10 mcg/dose vial, it would be difficult to add the entire volume of diluent into the vial, and the preparer will likely feel resistance.						
Blue caps	**Multi dose:** If an attempt is made to dilute the 10 mcg/dose dispersion for injection vial (dark blue cap), the user would immediately feel resistance to the addition of any further volume, because the filled volume is 2.25 mL and therefore, there is little remaining physical space to add additional diluent to the vial. **Single dose:** The filled volume for the light blue cap presentation is 0.48 mL because it contains 1 dose for extraction. If diluted with sodium chloride 9 mg/mL (0.9%) solution by mistake, the user would be able to extract multiple doses and the product would be over diluted and not achieve the appropriate dose level if administered.						

Table 67. Vaccine Presentation Characteristics - 6 months through 4 years

INN	Tozinameran	Tozinameran/ Famtozinameran	Raxtozinameran
Name	Comirnaty 3 mcg/dose DILUTE BEFORE USE Maroon cap	Comirnaty Original/Omicron BA.4-5 DILUTE BEFORE USE Maroon cap	Comirnaty Omicron XBB.1.5 DILUTE BEFORE USE Maroon Cap
Dose	3 mcg (with dilution)	1.5/1.5 mcg (with dilution)	3 mcg (with dilution)
Vial cap color and Label with Color Border	Maroon	Maroon	Maroon
Dose Volume	0.2 mL	0.2 mL	0.2 mL
Amount of Diluent Needed per Vial	2.2 mL	2.2 mL	2.2 mL
Fill Volume	0.4 mL	0.4 mL	0.4 mL
Doses per vial	10 doses per vial (after dilution)	10 doses per vial (after dilution)	10 doses per vial (after dilution)
Formulation	Tris sucrose	Tris sucrose	Tris sucrose
Maroon caps	If the contents of the vial are not diluted with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution, the user would only be able to extract approximately 1 dose instead of 10 doses because the vial fill volume is 0.4 mL. If 1.8 mL of diluent (purple cap amount) or 1.3 mL of diluent (orange cap amount) were used, this would be an under dilution and would also reduce the number of doses able to be extracted from the vial, which might indicate to the HCP that there had been an error in preparation.		

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 and a coloured border corresponding to the associated vials for the dose, were made available to support documentation of the batch/lot on the Traceability and Vaccination Reminder card and vaccinee medical records. 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 2025: 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 resources and referenced 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 15 studies, of which 4 global, 4 in Europe only, 5 in US only, 2 in US and Canada. There are 6 interventional studies (C4591007, C4591015, C4591024, C4591031, C4591044, C4591048), 2 Low-Interventional studies (C4591036 and WI255886) and 7 non-interventional studies (6 safety and 1 effectiveness), summarised in the table below and further detailed in Table 68 and Table 69.

Study Number	Country	Interventional/ non-Interventional/ Low-Interventional	Purpose
C4591007	Global	Interventional	Safety
C4591015	Global	Interventional	Safety
C4591024[a] (former Safety and immunogenicity in high-risk adults)	Global	Interventional	Safety
C4591031	Global	Interventional	Safety Effectiveness
C4591044	US	Interventional	Safety Effectiveness[b]
C4591048	US	Interventional	Safety Effectiveness[b]
C4591009	US	Non-Interventional	Safety
C4591021 (former ACCESS/VAC4EU)	EU	Non-Interventional	Safety
C4591022	US/CA	Non-Interventional	Safety
C4591038 (former C4591021 substudy)	EU	Non-Interventional	Safety
C4591014	US	Non-Interventional	Effectiveness[b]
WI255886	EU[d]	Low-Interventional	Effectiveness[b]
C4591036 (former Pediatric Heart Network)	US/CA	Low-Interventional	Safety
C4591051	US	Non-Interventional	Safety
C4591052	EU	Non-Interventional	Safety

Study Number	Country	Interventional/ non-Interventional/ Low-Interventional	Purpose

a. 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

b. Vaccine effectiveness is not a safety concern.

c. The study does not involve any administration of vaccine or other Pfizer products but since a specimen collection procedure is required per protocol, this qualifies this study as 'low-interventional'.

d. United Kingdom.

Study BNT162-01 was completed and final CSR was submitted on 07 August 2023 (Procedure EMEA/H/C/005735/II/0187).

Study WI235284 was completed, and final CSR was submitted on 30 June 2023 (Procedure NEMEA/H/C/005735/II/0186/G).

Study C4591001 was completed, and final CSR is submitted on 09 August 2023 (Procedure EMEA/H/C/005735/II/0188/G).

Non-Interventional Post Approval Safety Studies (7)

The MAH proposes 7-complementary studies of real-world safety of COVID-19 mRNA vaccine that use multiple data sources and study designs. These are described in Table 68 below which includes the proposed post-approval safety studies that will be conducted in the EU and US.

- 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 (formerly 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.

- Study C4591051 is a bivalent BNT162b2 (original/Omi BA.4/BA.5) safety surveillance study to be conducted using secondary data from administrative claims and electronic health records from data research partners participating in the US Sentinel System.

- Study C4591052 is a bivalent BNT162b2 (original/Omi BA.1) and bivalent BNT162b2 (original/Omi BA.4/BA.5) 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.

In addition to the studies in the EU, in support of the US BLA and sBLA applications, Pfizer is conducting 2 US studies and 1 US/CA for safety surveillance of COVID 19 mRNA. These studies include:

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

- 1 low-interventional study using primary data from the Pediatric Heart Network (PHN), a NIH-funded consortium of leading research hospitals across the US, Canada, and other countries that conducts research in cardiovascular disease, 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 pregnant women who are unvaccinated (C4591022).

The protocols for the safety studies in the US (C4591009, and in US/CA C4591022) were added in Annex 3 Part C.

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

Studies C4591021(EU), C4591009 (US), C4591051 (US) and C4591052 (EU) 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 ongoing studies C4591009, 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.

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.

A long-term primary data collection low-interventional 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.

In addition, the protocol of study C4591036 has been amended to include evaluation of individuals receiving additional approved doses, including the bivalent Omicron-modified vaccine. Additionally, the MAH has determined to not update the study C4591021, as accepted by the FDA and committed instead to conduct a standalone post-authorization observational safety study (C4591052) to evaluate the bivalent omicron-modified vaccine.

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) 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 low-interventional 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 6 of the real-world safety studies (C4591009, C4591021 [former ACCESS/VAC4EU] C4591022, C4591051 and C4591052), described in Table 68.

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 68 and Table 69).

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 (2)

Pfizer is conducting, 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 determination of 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[14] and WI255886) added. The harmonisation of study definitions across these 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. The two studies, C4591014 and WI255886, will also assess the effectiveness of bivalent Omicron-modified vaccines following their introduction.

[14] Study WI235284 was completed, and final CSR was submitted on 30 June 2023 (Procedure NEMEA/H/C/005735/II/0186/G). This study is removed from PART III.2.

Table 68. Additional Pharmacovigilance Activities

Study Number ***Country (ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
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 COVID-19 in healthy children and young adults. Interventional *Ongoing*	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.	Interim CSR submission:	30-Dec-2023[15]
					Final CSR submission:	30-Apr-2024[16]
C4591009 US	A non-interventional post approval safety study Pfizer-BioNTech COVID-19 vaccine in the United States. Non-Interventional *Ongoing*	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	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.	Protocol submission:	31-Aug-2021
					Protocol amendment submission:	11-Jul-2022

[15] As per approval of Justification milestone extension (EMEA/H/C/005735/X/0176)

[16] The change of the milestone was endorsed by EMA on 19 Apr 2023 (PAM-MEA-043.1)

Table 68. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
		electronic health records and claims data from data partners participating in the Sentinel System.		This study will include an analysis of individuals who receive a booster dose of the Pfizer-BioNTech COVID-19 vaccine.	Monitoring report 1 submission:	31-Oct-2022
					Interim Analysis submission:	30-Apr-2024[17]
					Final CSR submission:	31-Mar-2026[18]

[17] As per approval of PAM-MEA-037.5 (dated 09 Nov 2023) the ISR for C4591009 will be delayed to 30 Apr 2024 due to cybersecurity breach.

[18] FDA requested a protocol amendment to incorporate analyses in the 6 months- 4 years group. As part of the amendment, there were changes to the end of data collection and final study report milestone dates. Removal of the milestone for the second monitoring report is proposed due to the anticipated diminished value of the report relative to the planned interim study report to be submitted to both the EMA and US FDA by 30 April 2024.

Table 68. 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 *Completed*	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:	31-Jul-2024[19]

[19] Due to limited lab capacity and competing priorities on the COVID-19 programme, the serology data for Study C4591015 and C4591030 will not be available for submission by the current final CSR RMP milestone deadlines (30 April 2023 and 28 February, respectively). On 07 Feb 2023 (seq0490) via PAM-MEA-018.4 a joint study C4591015 + C4591030 justification has been submitted to EMA stating that final CSR for both 1015 & 1030 will be provided by 31 July 2024. The procedure MEA-018.4 is approved.

Table 68. 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). Non-Interventional *Ongoing*	To determine the effectiveness of COVID-19 mRNA vaccine and of the bivalent Omicron-modified vaccine when administered outside of the clinical setting. To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction, in all authorized age groups.	Non-interventional study (test-negative design) of individuals presenting with symptoms of potential COVID-19 illness in a real-world setting.	Individuals ≥ 6 months of age with acute respiratory illness admitted to the emergency department or hospital.	Final CSR submission:	30-Jun-2023
					Protocol amendment (for bivalent Omicron-modified vaccine) submission:	04-Jan-2023
					Final CSR (for bivalent Omicron-modified vaccine) submission:	30-Jun-2024
WI255886 Ex-EU[b]	Avon Community Acquired Pneumonia Surveillance Study. A pan-pandemic acute lower respiratory tract disease surveillance study. Low-Interventional[a] *Ongoing*	To determine the effectiveness of COVID-19 mRNA vaccine and of the bivalent Omicron-modified vaccine when administered outside of the clinical setting. To estimate the effectiveness of COVID-19 mRNA vaccine against	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 68. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
		hospitalisation for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction in individuals 18 years of age and older.			Protocol amendment (for bivalent Omicron-modified vaccine) submission:	15-Dec-2022[20]
					Final CSR (for bivalent Omicron-modified vaccine) submission:	30-Jun-2024
C4591024 (former Safety and immunogenicity in high-risk adults) Global	A Phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age. Interventional *Ongoing*	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal disease).	Open uncontrolled.	High risk individuals including frail, those having autoimmune disease, chronic renal disease and immunocompromising conditions.	Protocol submission:	30-Jun-2021
					Final CSR submission:	31-Jul-2024[21]

[20] Actual submission date (PAM-MEA-025.3)

[21] 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. Due to limited lab capacity and competing priorities on the COVID-19 programme, the serology data for the final CSR for study C4591024 will not be available for submission by the current RMP milestone deadline (30 June 2023). Based on the PAM-MEA-016.5 outcome (dated 14 Sep 2023) the submission of the final CSR for study C4591024 is delayed to 31 July 2024.

Table 68. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type ***Study Status***	Rationale and Study Objectives	Study design	Study populations	Milestones	
C4591021 (former ACCESS/VAC4EU) EU	Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech. Coronavirus Disease 2019 (COVID-19) vaccine. Non-Interventional *Ongoing*	Assessment of potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis after being vaccinated with COVID-19 mRNA vaccine, including individuals less than 12 years of age. Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.	Secondary database analysis of observational data to assess potential increased risk of adverse events of special interest (AESI and other clinically significant events among COVID-19 vaccine recipients in the EU. This study will include an analysis of individuals who receive booster dose of the Pfizer-BioNTech COVID-19 vaccine including the bivalent Omicron-modified vaccine if feasible.	EU General population (all ages).	Protocol amendment submission (booster dose):	31-Dec-2021[22]
					Final CSR submission:	20-Dec-2024[23]

[22] PAM-MEA-017.2, submitted on 04.01.2022 -submission date extension from 31.12.2021 to 04.01.2022 previously agreed with EMA, protocol amendment 1 was submitted and the outcome was received on 24.03.2022.

[23] 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. PA#4 proposed final CSR milestone extension change from 30 September 2024 to 20 December 2024.

Table 68. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
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 *Ongoing*	Assessment of the clinical course (treatment, survival, hospitalisations, long-term cardiac outcomes) of myocarditis and pericarditis among individuals diagnosed with myocarditis and/or pericarditis after receiving at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination, using a cohort study design.	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
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	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	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	Pregnant women and infant outcomes	Interim reports submission:	12-Apr-2022[24]
						31-Jan-2023
						31-Jan-2024

[24] Submission eCTD

Table 68. Additional Pharmacovigilance Activities

Study Number ***Country (ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
	(OTIS)/MotherToBaby Pregnancy Registry. Non-Interventional *Ongoing*	small for age postnatal growth to one year of age, relative to pregnant women who received no COVID-19 vaccines during pregnancy.	pregnant women who are unvaccinated.		Final CSR submission:	28-Feb-2026[25]
C4591036 (former Pediatric Heart Network Study) US/Canada	Low-Interventional Cohort Study of Myocarditis/Pericarditis Associated With COMIRNATY in Persons Less Than 21 Years of Age Low-Interventional *Ongoing*	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 including myocarditis after the bivalent Omicron-modified vaccine.	Prospective cohort study. This study will include an analysis of individuals who receive booster dose of the Pfizer-BioNTech COVID-19 vaccine including the bivalent Omicron-modified vaccine, if feasible.	Patients <21 years presenting to PHN sites after receiving any dose of BNT162b2 including the bivalent Omicron-modified vaccine, if feasible and who were diagnosed with myocarditis / pericarditis as well as individuals not vaccinated with myocarditis/pericarditis.	Protocol submission:	30-Nov-2021
					Protocol amendment submission:	15-Dec-2022
					6-monthly interim study report:	30-June-2023

[25] C4591022 milestone changed due to additional follow-up time needed to capture newly recruited subjects due to FDA 16 Sep 2021 request to increase sample size. Justification submitted via EMEA/H/C/005735/IB/0204 procedure.

Table 68. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
					Final CSR submission:	28-Feb-2031[26]
C4591031 Substudy E Global	An interventional, randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of high-dose BNT162b2 OMI (60 µg), high-dose BNT162b2 (60 µg), and a high-dose combination of BNT162b2	To describe the safety and tolerability profile of BNT162b2 (30 and 60 µg), BNT162b2 OMI (30 and 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants >55 years of age.	The sentinel-cohort participants randomized to the combination BNT162b2 and BNT162b2 OMI groups will be administered a suspension containing a mixture of	Participants: > 55 years of age 18- to 55 years of age	Interim reports submission (> 55 y):	31-Aug-2022
					Interim reports submission (18 – to 55 y):	31-Oct-2022

[26] The date of the final report has been extended based on the FDA's requirement to increase the sample size for Cohort 1 to 300 participants; this was also endorsed by EMA on 16 May 2022; PAM-MEA-041.1 was submitted on 31 July 2023 to provide protocol amendment #3, PAM-MEA-041.3 outcome (dated 12 October 2023) with reference to submitted PA #3 (PAM-MEA-041.4) endorsed C4591036 final CSR delay from 14 Nov 2029 to 28 February 2031.

Table 68. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
	OMI and BNT162b2 (30 µg of each), compared to BNT162b2 OMI 30 µg, BNT162b2 30 µg, and a combination of BNT162b2 OMI and BNT162b2 (15 µg of each), given as a fourth dose. Interventional *Ongoing*	To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in participants 18 to 55 years of age.	BNT162b2 WT and BNT162b2 OMI prepared from 2 separate vials at the investigator site. Participants in the expanded cohort who are randomized to the combination BNT162b2 and BNT162b2 OMI groups will receive the preformulated product containing BNT162b2 WT and BNT162b2 OMI		6M Final CSR submission (>18 y):	31-May-2024 [27]

[27] Final CHMP AR for PAM-MEA-058.1 (study 1031 SSE) received on 31 March 2023 confirming new proposed milestone.

Table 68. Additional Pharmacovigilance Activities

Study Number ***Country (ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
C4591044 US	An Interventional, Randomized, Active-Controlled, Phase 2/3 Study to Investigate the Safety, Tolerability, and Immunogenicity of Bivalent BNT162b RNA-Based Vaccine Candidates as A Booster Dose In COVID-19 Vaccine–Experienced Healthy Individuals Interventional *Ongoing*	Study boosting strategies against variants of concern. To describe the safety/tolerability and immune response to BNT162b5 Bivalent and BNT162b2 Bivalents given as a 2nd booster dose to COVID-19-vaccine-experienced participants ≥12 years of age	Cohort 1: randomized, active-controlled, observer-blind study Participants 18-55 years of age will be randomized at a ratio of 1:1 to receive a single 30 µg dose of 1 of the 2 study interventions: • BNT162b5 Bivalent (WT/OMI BA.2) • BNT162b2 Bivalent (WT/OMI BA.1) Cohort 2 (PA1): Participants 12 through 17 years of age will receive a single dose of bivalent	Healthy male and female participants ≥12 years of age. Stable chronic conditions including stable treated HIV, HBV and HCV allowed.	Protocol submission: Protocol amendment 1 submission: Protocol amendment 2 submission:	14-Jun-2022 28-Jul-2022 23-Sep-2022

Table 68. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
			BNT162b2 (original/Omi BA.4/BA.5) 30 µg as a second booster dose (open label). Participants 18-55 and >55 years of age will be randomized 1:1 within each age group to receive either bivalent BNT162b2 (original/Omi BA.4/BA.5) at 30 µg or 60 µg as a second booster dose (observer-blind).		Final CSR submission[28]	30-Sep-2024
C4591048 US Brazil, South Africa	A master phase 1/2/3 protocol to investigate the safety, tolerability, and immunogenicity of bivalent	To study up to four doses of variant-adapted BNT162b2 against variants of concern.	SSA Ph1: 3-dose bivalent series in COVID-19 vaccine-naïve participants 6	6 months to < 12 years (SSB, SSC, SSD).	Protocol submission	10-Oct-2022

[28] The original milestone of the final CSR for Study C4591044 was based upon the inclusion of 3 cohorts. Since then, an additional cohort has been added, although only cohorts 2 and 3 are endorsed EMA commitments (PAM-MEA-059.3). The final CSR will be available for submission to EMA by 30 September 2024.

Table 68. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study design**	**Study populations**	**Milestones**	
	BNT162b2 RNA - based vaccine candidate(s) in healthy children. Interventional *Ongoing*	To describe the safety/tolerability and immune response to variant-adapted BNT162b2.	months to <5 years, followed by a fourth dose with BNT162b2 (Omi XBB.1.5). SSA Ph2/3: 2-dose series or single-dose BNT162b2 (Omi XBB.1.5) to COVID-19 vaccine-naïve participants 6 months to <5 years. SSB, SSC, SSD: 3rd and/or 4th dose to COVID-19-vaccine-experienced participants 6 months to < 12 years of age. SSE: Single dose BNT162b2 (Omi XBB.1.5) in COVID-19 vaccine naïve participants 2 to <5 and 5 to <12 years.	6 months to <4 years 3 months (SSA Ph1). 6 months to <5 years (SSA ph 2/3). 2 to <5 years (SSE) 5 to <12 years (SSE)	Final CSR submission	20-Dec-2025[29]

[29] Protocol amendment 4 of study C4591048 (PAM-MEA-057.5) was developed based on the response to the recommendation from the FDA to simplify the COVID-19 vaccine series, including in individuals under 12 years of age. This protocol amendment 4 resulted in updates to the study design which changed the final CSR submission from 31 May 2025 to 20 December 2025.

Table 68. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type ***Study Status***	Rationale and Study Objectives	Study design	Study populations	Milestones	
C4591051 US	Post-Approval Safety Study of Pfizer-BioNTech Bivalent COVID-19 Vaccine in the United States Non-Interventional *Planned*	To ensure comprehensive understanding of real-world safety of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine in large samples of general US populations.	This observational study will capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the COVID-19 bivalent Omicron-modified vaccine since its availability under an EUA using electronic health records and claims data from data partners participating in the Sentinel System	General population	Protocol synopsis submission:	31 Jan 2023
					Protocol submission	31 May 2023
					Final CSR submission	31-Jan-2027[30]
C4591052 EU	Post-Authorisation Safety Study of Comirnaty Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5 in Europe Non-Interventional *Planned*	To ensure comprehensive understanding of real-world safety of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine in large samples of general EU populations.	This observational study will capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the COVID-19 bivalent Omicron-modified	General population	Protocol synopsis submission:	04-Jan-2023
					Protocol submission	30-Apr-2023
					Final CSR submission	30-Apr-2026

[30] C4591051 PA justification submitted via EMEA/H/C/005735/IB/0204 procedure.

Table 68. Additional Pharmacovigilance Activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
			vaccine since its availability.			

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

III.3. Summary Table of Additional Pharmacovigilance Activities

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

Table 69. 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					
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.	Long term safety data.	Interim CSR submission:	30 Dec 2023[15]
				Final CSR submission:	30-Apr-2024[16]
C4591009 *Ongoing*	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 Long term safety data	Protocol submission:	31-Aug-2021
				Protocol amendment submission:	11-Jul-2022
				Monitoring report 1 submission:	31-Oct-2022
				Interim Analysis submission:	30-Apr-2024[17]
				Final CSR submission:	31-Mar-2026[18]

Table 69. On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) Status (*planned/on-going*)	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
C4591015 *Completed*	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:	31-Jul-2024 [19]
C4591014 *Ongoing*	US	To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction in all authorized age groups.	Not Applicable[c].	Final CSR submission:	30-Jun-2023
				Protocol amendment (for bivalent Omicron-modified vaccine) submission:	04-Jan-2023
				Final CSR (for bivalent Omicron-modified vaccine) submission:	30-Jun-2024

Table 69. On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) Status (*planned/on-going*)	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
WI255886 *Ongoing*	Ex-EU[a,b]	To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction in individuals 18 years of age and older.	Not Applicable[c].	Final CSR submission:	30-Jun-2023
				Protocol amendment (for bivalent Omicron-modified vaccine) submission:	15-Dec-2022[20]
				Final CSR (for bivalent Omicron-modified vaccine) submission:	30-Jun-2024
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:	31-Jul-2024[21]
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 including individuals less than 12 years of age.	Myocarditis and Pericarditis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy	Protocol amendment submission (booster dose):	31-Dec-2021[22]

Table 69. 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
		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.	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:	20-Dec-2024[23]
C4591038 (former C4591021 substudy) *Ongoing*	EU	To describe the clinical course (treatment, survival, hospitalisations, long-term cardiac outcomes) of myocarditis and pericarditis among individuals diagnosed with myocarditis and/or pericarditis after receiving at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination, using a cohort study design.	Myocarditis and Pericarditis Long term safety data.	Protocol submission:	31-Jan-2022
				Final CSR submission:	30-Sep-2024
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, relative to pregnant women who received no COVID-19 vaccines during pregnancy.	Use in pregnancy.	Interim reports submission:	12-Apr-2022[24]
					31-Jan-2023
					31-Jan-2024

Table 69. 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
				Final CSR submission:	28-Feb-2026[25]
C4591036 (former Pediatric Heart Network Study) *Ongoing*	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 including myocarditis after the bivalent Omicron modified vaccine.	Myocarditis/pericarditis Long term safety data.	Protocol submission:	30-Nov-2021
				6-monthly interim study report:	30-June-2023
				Protocol amendment submission:	15-Dec-2022
				Final CSR submission:	28-Feb-2031[26]
C4591031 Substudy E *Ongoing*	Global	To describe the safety and tolerability profile of BNT162b2 (30 and 60 µg), BNT162b2 OMI (30 and 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants >55 years of age. To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in participants 18 to 55 years of age.	Reactogenicity as partial proxy to the general safety profile	Interim reports submission (> 55 y):	31-Aug-2022
				Interim reports submission (18 - to 55 y):	31-Oct-2022
				6M Final CSR submission (>18y):	31-May-2024

Table 69. 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**
C4591044 *Ongoing*	US	To describe the safety/tolerability and immune response to BNT162b5 Bivalent and BNT162b2 Bivalents given as a 2nd booster dose to COVID-19-vaccine-experienced participants ≥12 years of age.	Not applicable[c] Reactogenicity as partial proxy to the general safety profile	Protocol Submission:	14-Jun-2022
				Protocol amendment 1 submission:	28-Jul-2022
				Protocol amendment 2 submission:	23-Sep-2022
				Final CSR submission[28]:	30-Sep-2024
C4591048 *Ongoing*		To describe the safety/tolerability and immune response to variant-adapted BNT162b2 given as:	Not applicable[c]	Protocol Submission:	10-Oct-2022

Table 69. 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
	US, Brazil, South Africa	SSA Ph1: 3-dose bivalent series in COVID-19 vaccine-naïve participants 6 months to <5 years, followed by a fourth dose with BNT162b2 (Omi XBB.1.5). SSA Ph2/3: 2-dose series or single-dose BNT162b2 (Omi XBB.1.5) to COVID-19 vaccine-naïve participants 6 months to <5 years. SSB, SSC, SSD: 3rd and/or 4th dose to COVID-19-vaccine-monovalent experienced participants 6 months to < 12 years of age. SSE: Single dose BNT162b2 (Omi XBB.1.5) in COVID-19 vaccine naïve participants 2 to < 5 and 5 to <12 years.		Final CSR submission:	20-Dec-2025[29]
C4591051 *Planned*	US	Post-approval observational studies using real-world data are needed to assess the association between COVID-19 bivalent Omicron-modified Vaccine and safety events of interest among persons administered the vaccine in the overall US population.	Myocarditis/pericarditis Use in pregnancy Use in immunocompromised patients Long-term safety data	Protocol synopsis submission:	31-Jan-2023
				Protocol submission	31-May-2023

Table 69. 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
		This observational study will capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the Pfizer-BioNTech COVID-19 bivalent Omicron-modified Vaccine since its availability under an EUA using electronic health records and claims data from data partners participating in the Sentinel System.		Final CSR submission	31-Jan-2027[30]
C4591052 *Planned*	EU	Post-approval observational studies using real-world data are needed to assess the association between Pfizer-BioNTech COVID-19 bivalent Omicron-modified Vaccine and safety events of interest among persons administered the vaccine in the overall EU population. This observational study will capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the COVID-19 bivalent Omicron-modified Vaccine since its availability.	Myocarditis/pericarditis Use in pregnancy AESI-based safety events of interest including vaccine associated enhanced disease 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	Protocol synopsis submission:	04-Jan-2023
				Protocol submission	30-Apr-2023
				Final CSR submission	30-Apr-2026

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

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 70. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Important Identified Risk	
Myocarditis and Pericarditis	Routine risk communication: SmPC section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Important Potential Risk	
None	
Missing Information	
Use in pregnancy and while breast feeding	Routine risk communication: SmPC section 4.6 Fertility, pregnancy and lactation PL section 2. What you need to know before you receive Comirnaty, Comirnaty Original/Omicron BA.1 (15/15 mcg) and Comirnaty Original/Omicron BA.4-5 (15/15 mcg) and Comirnaty Omicron XBB.1.5. 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 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.

Table 70. Description of Routine Risk Minimisation Measures by Safety Concern

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.
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 per below.

Table 71. 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 72. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis and pericarditis	Routine risk minimisation measures: SmPC sections 4.4. and 4.8. Additional risk minimisation measures: DHCP letter and communication plan (see V.2 and Annex 6).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: *Studies (Final CSR Due Date)* C4591009 (31-Mar-2026) C4591021 (former ACCESS/VAC4EU) (20 Dec-2024). C4591038 (former C4591021 substudy) (30-Sep-2024) C4591036 [former Pediatric Heart Network study] (28-February 2031) C4591051 (31-Jan 2027) C4591052 (30-Apr-2026)
Use in pregnancy and while breast feeding	Routine risk minimisation measures: SmPC section 4.6; PL section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: *Studies (Final CSR Due Date)* C4591009[a] (31-Mar-2026) C4591015 (31-Jul-2024)[19] C4591021 (former ACCESS/VAC4EU)[a] (20 Dec-2024). C4591022[a] (28-Feb-2026) C4591051[a] (31-Jan 2027) C4591052[a] (30-Apr-2026)
Use in immunocompromised patients	Routine risk minimisation measures: SmPC sections 4.4 and 5.1. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: *Studies (Final CSR)* C4591009 (31-Mar-2026) C4591021 (former ACCESS/VAC4EU) (20 Dec 2024) C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)[21] C4591051 (31-Jan-2027) C4591052 (30-Apr-2026)

Table 72. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: *Studies (Final CSR Due Date)* C4591021 (former ACCESS/VAC4EU) (20 Dec 2024) C4591024 (former Safety and immunogenicity in high-risk adults) (31-Jul-2024)[21] C4591052 (30-Apr-2026)
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: *Studies (Final CSR Due Date)* C4591021 (former ACCESS/VAC4EU) (20 Dec-2024) C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)[21] C4591052 (30-Apr-2026)
Long term safety data	Routine risk minimisation measures: None. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: *Studies (Final CSR Due Date)* C4591007 (30-Apr-2024) C4591009 (31-Mar-2026) C4591021 (former ACCESS/VAC4EU) (20 Dec 2024). C4591038 (former C4591021 substudy) (30-Sep-2024) C4591036 (former PHN) (28-Feb-2031) C4591051 (31-Jan-2027) C4591052 (30-Apr-2026)

a. Please note that studies C4591009, C4591021 (former ACCESS/VAC4EU) and C4591022, C4591051 and C4591052 address only “Use in pregnancy” and not “Breast feeding”.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Comirnaty, Comirnaty Original/Omicron BA.1 (15/15 micrograms) Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB1.5.

This is a summary of the risk management plan (RMP) for Comirnaty, for Comirnaty Original/Omicron BA.1 (15/15 micrograms) for Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5. The RMP details important risks of Comirnaty, of Comirnaty Original/Omicron BA.1 (15/15 micrograms), of Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5, how these risks can be minimised, and how more information will be obtained about Comirnaty's, Comirnaty Original/Omicron BA.1 (15/15 micrograms) Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 risks and uncertainties (missing information).

Comirnaty, Comirnaty Original/Omicron BA.1 (15/15 micrograms), Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Comirnaty, Comirnaty Original/Omicron BA.1 (15/15 micrograms) and Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 should be used.

This summary of the RMP for Comirnaty, for Comirnaty Original/Omicron BA.1 (15/15 micrograms) Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 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, Comirnaty Original/Omicron BA.1 (15/15 micrograms) and Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 RMP.

I. The Medicine and What It Is Used For

Comirnaty, Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 are indicated for active immunisation to prevent COVID-19 caused by SARS CoV 2 virus, in individuals 6 months of age and older.

Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older (see SmPC for the full indication).

All contain nucleoside-modified messenger RNA encapsulated in lipid nanoparticles as the active substance and are given intramuscularly.

Further information about the evaluation of Comirnaty’s, of Comirnaty Original/Omicron BA.1 (15/15 micrograms) of Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 benefits can be found in Comirnaty’s, Comirnaty Original/Omicron BA.1 (15/15 micrograms) Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 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, of Comirnaty Original/Omicron BA.1 (15/15 micrograms) of Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 together with measures to minimise such risks and the proposed studies for learning more about Comirnaty's, Comirnaty Original/Omicron BA.1 (15/15 micrograms) Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 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, of Comirnaty Original/Omicron BA.1 (15/15 micrograms) and of Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Comirnaty, of Comirnaty Original/Omicron BA.1 (15/15 micrograms) of Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 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, of Comirnaty Original/Omicron BA.1 (15/15 micrograms), Comirnaty Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5. 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 73. List of Important Risks and Missing Information

Important identified risks	Myocarditis and Pericarditis
Important potential risks	None
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
	Long term safety data

II.B Summary of Important Risks

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

Table 74. 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 C4591021 (former ACCESS/VAC4EU) C4591038 (former C4591021 sub-study) C4591036 (former Pediatric Heart Network study) C4591051 C4591052 See Section II.C this summary for an overview of the post-authorisation development plan.

Table 75. 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: None.
Additional pharmacovigilance activities	C4591009[a] C4591015 C4591021 (former ACCESS/VAC4EU)[a] C4591022[a] C4591051[a] C4591052[a] See Section II.C of this summary for an overview of the post-authorisation development plan.

a. Please note that studies C4591009, C4591011, C4591021 (former ACCESS/VAC4EU) and C4591022, C4591051 and C4591052 address only "Use in pregnancy" and not "Breast feeding".

Table 76. Missing Information: Use in Immunocompromised Patients

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 5.1. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	C4591009 C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and Immunogenicity in high-risk adults) C4591051 C4591052 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 77. Missing Information: Use in Frail Patients with Co-morbidities (eg. 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: None.
Additional pharmacovigilance activities	C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and immunogenicity in high-risk adults) C4591052 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 78. Missing Information: Use in Patients with Autoimmune or Inflammatory Disorders

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and immunogenicity in high-risk adults) C4591052 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 79. Missing Information: Long Term Safety Data

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	C4591007 C4591009 C4591021 (former ACCESS/VAC4EU) C4591038 (former C4591021 substudy) C4591036 (former PHN) C4591051 C4591052 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

None.

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

Study	Purpose of the study
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.
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.

Study	Purpose of the study
C4591015	To assess safety and immunogenicity in pregnant women In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.
C4591014	To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction in all authorized age groups.
WI255886	To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction in individuals 18 years of age and older.
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, including individuals less than 12 years of age. 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 describe clinical course (treatment, survival, hospitalisations, long-term cardiac outcomes) of myocarditis and pericarditis among individuals diagnosed with myocarditis and/or pericarditis after receiving at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination, using a cohort. study.
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 relative to pregnant women who received no COVID-19 vaccines during pregnancy.
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 including myocarditis after the bivalent Omicron modified vaccine.
C4591031 Substudy E	To describe the safety and tolerability profile of BNT162b2 (30 µg or 60 µg), BNT162b2 OMI (30 µg or 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2 experienced participants >55 years of age and experienced participants 18-to 55 years of age
C4591044	To describe the safety/tolerability and immune response to BNT162b5 Bivalent and BNT162b2 Bivalents given as a 2nd booster dose to COVID-19-vaccine-experienced participants ≥12 years of age.
C4591048	To investigate the safety, tolerability, and immunogenicity of variant-adapted BNT162b2 RNA-based vaccine candidate(s) in healthy children.
C4591051	To ensure comprehensive understanding of real-world safety of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine in large samples of general US populations.
C4591052	To ensure comprehensive understanding of real-world safety of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine in large samples of general EU populations.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Table of contents

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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

Pfizer-BioNTech COVID-19 Vaccine Multisystem Inflammatory Syndrome in Pediatric and Adults Reaction 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. Was the patient admitted to hospital (please state if ICU admission)? Please provide admission and discharge dates.

3. CLINICAL MANIFESTATION

Fever: Measured temperature: Celsius: Fahrenheit:
Duration of fever (e.g., 3 days):

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: ____

Heart 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: ____

4. 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	☐	☐	☐				
Other	☐	☐	☐				

5. 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)	☐	☐	☐		

6. 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	☐	☐	☐		

7. 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)

8. 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)

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

Version History

Version	Version Date	Summary of Revisions
2.0	03-Oct-2022	Updated to add question regarding hospital admission, correct typo under clinical manifestations, and add another line for "other" for the relevant labs question.
1.0	03-Oct-2022	Existing DCA converted to latest DCA format. Version 1 was never effective.

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.