# COMIRNATY, COMIRNATY ORIGINAL/OMICRON BA.1, COMIRNATY ORIGINAL/OMICRON BA.4-5 (COVID-19 mRNA VACCINE) RISK MANAGEMENT PLAN

RMP Version number: 9.0

Data lock point for this RMP: See below

| **Age group** | **Module SIII. Clinical Trial Exposure** | **Module SVII.3. Details of Important Risks** |
|---|---|---|
| 12 years of age and older booster dose of a bivalent Omicron - (BA.1 and BA.4-5) modified vaccine (BNT162b2 + BNT162b2 OMI 30 µg)[a] | Sentinel cohort 05 April 2022 and expanded cohort cut-off date: 16 May 2022 (C4591031 Substudy E).<br><br>11 March 2022 (C4591031 Substudy D – Cohort 2). | Sentinel cohort 05 April 2022 and expanded cohort cut-off date: 16 May 2022 (Pfizer Clinical Database C4591031 Substudy E).<br><br>11 March 2022 (Pfizer Clinical Database C4591031 Substudy D – Cohort 2).<br><br>30 June 2022 (Pfizer safety Database) |
| 6 months to <5 years (Primary series) | 16 July 2021 (Phase 1)<br>29 April 2022 (Phase 2/3) | 29 April 2022 (Pfizer Clinical Database – Study C4591007 Phase 2/3)<br><br>15 April 2022 (Pfizer Safety Database, non-CT dataset) |
| 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)<br><br>31 August 2022 (Pfizer Safety Database, for non-CT dataset) |
| 12-15 years of age, including severely immunocompromised (Primary series) | 13 March 2021 (Pfizer Clinical Database) | 30 September 2021 (Pfizer Safety Database, for CT dataset) |
| Booster (3rd) dose in 12 -15 years of age | N/A | 28 February 2022 (Pfizer Safety Database, both CT and non-CT datasets) |
| 16 years and older, including severely immunocompromised (Primary series) | 13 March 2021 (Pfizer Clinical Database)<br><br>23 October 2020 (BioNTech Clinical Database) | 30 September 2021 (Pfizer Safety Database, for CT dataset) |
| Booster (3rd) dose in 16 years and older[b] | 17 June 2021 (Pfizer Clinical Database) | 17 June 2021 (Pfizer Clinical Database, study C4591001)<br><br>28 February 2022 (Pfizer Safety Database, for non-CT dataset) |
| Post-Authorisation Experience: 18 June 2022 | | |

a. Detailed language is included in the proposed SmPC and in the Clinical Overview in support of Comirnaty Original/Omicron BA.1 and BA.4-5 (15/15) micrograms submissions
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: 04 November 2022

Rationale for submitting an updated RMP (v 9.0): to consolidate RMP v 8.0 and RMP v 7.2.

- RMP v 8.0 is a consolidated version that includes the 6 months to <2 years and 2 years to <5 years phase 1 and phase 2/3 data from interventional clinical study C4591007 for the line extension (from RMP v 5.1) and data that support the extension of the indication to ≥12 years of age to receive a booster dose of bivalent Omicron- (BA.4-5) modified vaccine (from RMP v 7.1).

- RMP v 7.2: includes data that support the extension of the indication to children 5 to 11 years of age to receive a dose of bivalent Omicron BA.4-5 modified vaccine, (Comirnaty Original/Omicron BA.4-5 (5/5 micrograms); in addition, the PRAC preliminary assessment request to remove Myocarditis and Pericarditis, Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) as safety concerns in study C4591048 is addressed.

Summary of significant changes in the 2 RMPs:

| RMP Part/Module | RMP 8.0<br>Major Changes | RMP 7.2<br>Major Changes |
|---|---|---|
| PART I PRODUCT(S) OVERVIEW | Addition of:<br>- Comirnaty Original/Omicron BA.4-5 (15/15 mcg)<br>- Comirnaty original paediatric population (6 month to 4 years of age) data according to the updated SmPC. | Addition of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) according to the updated SmPC. |
| PART II SAFETY SPECIFICATION | | |
| PART II.Module SI Epidemiology of the Indication(s) and Target Populations | Updated with new DLP and new data for Omicron variants and to lower the indication of Comirnaty original from 5 years to 6 months of age and older. | Updated to include the indication of Comirnaty original /Omicron BA.4-5 in individuals 5 years of age and older |
| PART II.Module SII Non-Clinical Part of the Safety Specification | Minor update with animal immunogenicity data for BA.4-5 | No changes made. |
| PART II.Module SIII Clinical Trial Exposure | Addition of text and CT exposure tables from Study C4591007 Phase 1 and Phase 2/3. | No changes made. |
| PART II.Module SIV Populations Not Studied in Clinical Trials | Updated with exposure from study C4591007. | Minor change in SIV.3 (for paediatric population) |

| RMP Part/Module | RMP 8.0<br>Major Changes | RMP 7.2<br>Major Changes |
|---|---|---|
| PART II.Module SV Post-Authorisation Experience | Updated with new DLP 18 June 2022. | No changes made |
| PART II.Module SVI Additional EU Requirements for the Safety Specification | No changes made. | No changes made. |
| PART II.Module SVII Identified and Potential Risks | Minor update on B/R of pregnancy/breast feeding and immunocompromised patients according to the updated SmPC for BA.4-5.<br><br>Updated to include reactogenicity for 6 months to less than 5 years old population.<br><br>Addition of data related to 6 months to less than 5 years old participants for the important risks of, myocarditis and pericarditis and VAED/VAERD and DLP revised as per table above. | The characterization of the important risks Myocarditis and Pericarditis and VAED/VAERD (non-CT data) was updated for the age group 5 to <12 years of age (booster 3rd dose) with new DLP as per table above. |
| PART II.Module SVIII Summary of the Safety Concerns | No changes made. | No changes made. |
| PART III PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES) | | |
| III.1 Routine Pharmacovigilance activities | Updated to add:<br>- Comirnaty Original/Omicron BA.4-5 (15/15 mcg) formulation in the vial differentiation description.<br>- the paediatric (6 month to 4 years of age) formulation in the vial differentiation description.<br><br>The term "educational materials" was rephrased to "resources and referenced materials" to comply the Assessment report on procedure EMEA/H/C/005735/II/0140. | Updated to add Comirnaty Original/Omicron BA.4-5 (5/5 mcg) formulation in the vial differentiation description. |

| RMP Part/Module | RMP 8.0<br>Major Changes | RMP 7.2<br>Major Changes |
|---|---|---|
| III.2 Additional Pharmacovigilance Activities<br>and<br>III.3 Summary Table of Additional Pharmacovigilance Activities | The Category 2 studies (C4591001 and C4591007) were reclassified as Category 3 based on the Renewal approval with cMA conversion to standard MA (EC decision: 10 October 2022).<br><br>Inclusion of 2 new interventional studies as additional PV activity: C4591031 and C4591044. For these studies 'Myocarditis and Pericarditis, Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)' were removed from the column Safety concerns addressed and replaced with "Reactogenicity as partial proxy to the general safety profile"<br><br>Addition of updated text for C4591014 and WI255886 that will also assess the effectiveness of the bivalent Omicron modified vaccines following their introduction.<br><br>Updates of other non-interventional studies (C4591012, C4591021, and C4591036) to be assessed for the feasibility of studying the bivalent Omicron modified vaccine. | Inclusion of 1 new interventional study as additional PV activity C4591048 to address: 'Myocarditis and Pericarditis, VAED/VAERD and Vaccine effectiveness however, as per PRAC pAR request received 19 October 2022, for study C4591048 'Myocarditis and pericarditis, and VAED/VAERD are removed as 'Safety concerns addressed.'<br><br>Addition of updated text in the study's objectives for C4591021, C4591014 and WI255886.<br><br>Milestones changed for studies C4591030 and C4591048; new milestone added for protocol amendment 2 of study C4591044. |
| PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES | No changes made. | No changes made. |
| PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES) | | |
| V.1 Routine Risk Minimisation Measures<br><br>V.2 Additional Risk Minimisation Measures<br><br>V.3 Summary of Risk Minimisation Measures | Updated based on the changes made in PART III. | Updated based on the changes made in PART III. |
| PART VI SUMMARY OF THE RISK MANAGEMENT PLAN | | |
| I The Medicine and What It Is Used For | Updated to include Comirnaty Original/Omicron BA.4-5 (15/15 mcg) | Updated to include Comirnaty Original/Omicron BA.4-5 (5/5 mcg) |

| RMP Part/Module | RMP 8.0<br>Major Changes | RMP 7.2<br>Major Changes |
|---|---|---|
| II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks | Updated to lower the indication of Comirnaty original from 5 years to 6 months of age and older<br><br>Updated based on the changes made in PART III and PART V. | Updated to lower the indication of Comirnaty original Omicron BA.4-5 from 12 years to 5 years of age and older.<br><br>Updated based on the changes made in PART III and PART V. |
| PART VII ANNEXES TO THE RISK MANAGEMENT PLAN | Annex 2: Studies/milestones updated<br>Annex 3: Addition of the 2 new studies C4591031 and C4591044<br>Annex 7 Addition of the updated Traceability Card<br>Annex 8: Changes to reflect the updates | Annex 2: Studies/milestones updated<br>Annex 3: Addition of study C4591044 in Part C.<br>Annex 8: Changes to reflect the updates |

Other RMP versions under evaluation:

None.

Details of the currently approved RMP

RMP version number: 8.0

Approved with procedure number: EMEA/H/C/005735/X/0138

Date of approval: 19 October 2022

QPPV name[1]: Barbara De Bernardi

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

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

## LIST OF ABBREVIATIONS

| Abbreviation | Definition of Term |
|---|---|
| ACIP | Advisory Committee on Immunisation Practices |
| AE | adverse event |
| AESI | adverse event of special interest |
| A:G | albumin:globulin |
| ALC-0315 | ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) |
| ALC-0159 | 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide |
| ARDS | acute respiratory distress syndrome |
| BALB/c | bagg albino |
| BC | Brighton Collaboration |
| 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 |
| 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 |
| EHR | electronic health records |
| EMA | European Medicines Agency |
| EUA | emergency use authorisation |
| EU | European Union |
| FDA | (US) Food and Drug Administration |
| GLP | good laboratory practice |
| HbA1c | glycated haemoglobin |
| HBV | hepatitis b virus |
| 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 |
| IL-4 | interleukin 4 |

| Abbreviation | Definition of Term |
|---|---|
| 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 |
| SMQ | standardised MedDRA query |
| SmPC | summary of product characteristics |
| SMSR | summary monthly safety report |
| SPEAC | Safety Platform for Emergency vACcines |
| SSR | summary safety report |
| SSE | substudy E |

| Abbreviation | Definition of Term |
|---|---|
| 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 |
| VAERD | vaccine-associated enhanced respiratory disease |
| 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).<br><br>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).<br><br>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). |
| **Pharmacotherapeutic group(s) (ATC Code)** | J07BX03 |
| **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:** | Chemical class<br><br>Nucleoside-modified messenger RNA is formulated in LNP |
| | Summary of mode of action<br><br>The nucleoside-modified messenger RNA in Comirnaty is formulated in LNPs, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19. |
| | Important information about its composition<br><br>**Comirnaty:**<br>is nucleoside-modified messenger RNA formulated in LNPs;<br>is a white to off-white frozen dispersion<br>(pH:6.9 – 7.9).<br><br>**Excipients for 30 micrograms/dose concentrate for dispersion for injection (PBS-Sucrose):**<br>((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)<br>2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)<br>1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)<br>cholesterol,<br>potassium chloride,<br>potassium dihydrogen phosphate,<br>sodium chloride, |

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| | disodium phosphate dihydrate,<br>sucrose,<br>water for injection<br>sodium hydroxide (for pH adjustment)<br>hydrochloric acid (for pH adjustment)<br><br>**Excipients for 30 micrograms/dose dispersion for injection (Tris-Sucrose):**<br>ALC-0315<br>ALC-0159<br>DSPC<br>cholesterol<br>trometamol<br>trometamol hydrochloride<br>sucrose<br>water for injection.<br><br>**Excipients for 10 micrograms/dose concentrate for dispersion for injection, Children 5 to 11 years and for 3 micrograms/dose concentrate for dispersion for injection, Infants and Children aged 6 months to 4 years (Tris-sucrose):**<br>ALC-0315<br>ALC-0159<br>DSPC<br>cholesterol<br>trometamol<br>trometamol hydrochloride<br>sucrose<br>water for injection<br><br>The Tris-sucrose formulation is based on the current approved vaccine except that the formulation buffer has been changed from phosphate buffered saline to Tris buffer without sodium chloride and potassium chloride while maintaining the same target pH.<br><br>**Comirnaty Original/Omicron BA.1:**<br>**Excipients for 15/15 micrograms/dose dispersion for injection (Tris-sucrose):**<br>ALC-0315<br>ALC-0159<br>DSPC<br>cholesterol<br>trometamol<br>trometamol hydrochloride<br>sucrose<br>water for injection<br><br>**Comirnaty Original/Omicron BA.4-5:**<br>**Excipients for 15/15 and 5/5 micrograms/dose dispersion for injection (Tris-sucrose):**<br>ALC-0315<br>ALC-0159<br>DSPC<br>cholesterol<br>trometamol<br>trometamol hydrochloride |

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| | sucrose<br>water for injection |
| **Hyperlink to the Product Information:** | Please refer to Module 1.3.1 of this submission |
| **Indication in the EEA** | Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 6 months of age and older.<br><br>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.<br><br>Comirnaty Original/Omicron BA.4-5 (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.<br><br>Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 5 years of age and older. |
| **Dosage in the EEA** | **Comirnaty PBS-Sucrose (30 micrograms/dose)**<br><br>*Primary vaccination course*<br><br>*Individuals 12 years of age and older:*<br>30 micrograms/dose concentrate for dispersion for injection is administered intramuscularly after dilution as a course of 2 doses (0.3 mL each). It is recommended to administer the second dose 3 weeks after the first dose.<br><br>*Severely immunocompromised aged 12 years and older*<br>A third primary course dose may be administered intramuscularly at least 28 days after the second dose to individuals who are severely immunocompromised.<br><br>*Interchangeability*<br>The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers to complete the primary course has not been established. Individuals who have received a dose of Comirnaty should continue to receive Comirnaty to complete the primary course.<br><br>Doses of Comirnaty 30 micrograms/dose concentrate for dispersion for injection after dilution (supplied in a vial with a purple cap) and Comirnaty 30 micrograms/dose dispersion for injection (supplied in a vial with a grey cap) are considered interchangeable.<br><br>*Booster dose*<br>A booster dose of Comirnaty should be administered intramuscularly as early as 3 months after the primary course with Comirnaty in individuals 12 years of age and older.<br>Comirnaty may also be given as a booster dose in individuals 18 years of age and older who have received a primary course comprised of another mRNA vaccine or adenoviral vector vaccine.<br><br>*Elderly*<br>No dosage adjustment is required in elderly individuals ≥ 65 years of age.<br><br>**Comirnaty Tris-sucrose (30 micrograms/dose)** |

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| | *Primary vaccination course*<br><br>*Individuals 12 years of age and older:*<br>Comirnaty is administered intramuscularly as a primary course of 2 doses (0.3 mL each). It is recommended to administer the second dose 3 weeks after the first dose.<br><br>*Severely immunocompromised aged 12 years and older*<br>A third primary course dose may be administered intramuscularly at least 28 days after the second dose to individuals who are severely immunocompromised.<br><br>*Interchangeability*<br>The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers to complete the primary course has not been established. Individuals who have received a dose of Comirnaty should continue to receive Comirnaty to complete the primary course.<br><br>Doses of Comirnaty 30 micrograms/dose concentrate for dispersion for injection after dilution (supplied in a vial with a purple cap) and Comirnaty 30 micrograms/dose dispersion for injection (supplied in a vial with a grey cap) are considered interchangeable.<br><br>*Booster dose*<br>A booster dose of Comirnaty should be administered intramuscularly as early as 3 months after the primary course with Comirnaty in individuals 12 years of age and older.<br><br>Comirnaty may also be given as a booster dose in individuals 18 years of age and older who have received a primary course comprised of another mRNA vaccine or adenoviral vector vaccine.<br><br>*Elderly population*<br>No dosage adjustment is required in elderly individuals ≥ 65 years of age.<br><br>**Comirnaty Tris-sucrose (10 micrograms/dose)**<br><br>*Children 5 to 11 years (i.e., 5 to less than 12 years of age*):<br>10 micrograms/dose is administered intramuscularly after dilution as a primary course of 2 doses (0.2 mL each). It is recommended to administer the second dose 3 weeks after the first dose.<br><br>*Severely immunocompromised aged 5 years and older*<br>A third primary course dose may be administered intramuscularly at least 28 days after the second dose to individuals who are severely immunocompromised.<br><br>*Interchangeability*<br>The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers to complete the primary course has not been established. Individuals who have received a dose of Comirnaty should continue to receive Comirnaty to complete the primary vaccination course.<br><br>**Comirnaty Tris-sucrose (3 micrograms/dose)**<br><br>*Infants and children 6 months to 4 years of age* |

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| | 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.<br><br>If a child turns 5 years old between their doses in the vaccination course, he/she should complete the series at the same 3 micrograms dose level.<br><br>**Comirnaty Original/Omicron BA.1 Tris-sucrose (15/15 micrograms/dose)**<br><br>The dose of Comirnaty Original/Omicron BA.1 is 0.3 mL given intramuscularly.<br><br>There should be an interval of at least 3 months between administration of Comirnaty Original/Omicron BA.1 and the last prior dose of a COVID-19 vaccine.<br><br>Comirnaty Original/Omicron BA.1 is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.<br><br>**Comirnaty Original/Omicron BA.4-5 Tris-sucrose (15/15 micrograms/dose)**<br><br>The dose of Comirnaty Original/Omicron BA.4-5 is 0.3 mL given intramuscularly.<br><br>There should be an interval of at least 3 months between administration of Comirnaty Original/Omicron BA.4-5 and the last prior dose of a COVID-19 vaccine.<br><br>Comirnaty Original/Omicron BA.4-5 is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.<br><br>**Comirnaty Original/Omicron BA.4-5 (5/5 micrograms/dose)**<br><br>The dose of Comirnaty Original/Omicron BA.4-5 is 0.2 mL given intramuscularly.<br><br>There should be an interval of at least 4 months between administration of Comirnaty Original/Omicron BA.4-5 and the last prior dose of a COVID-19 vaccine.<br><br>Comirnaty Original/Omicron BA.4-5 is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.<br><br>Comirnaty Original/Omicron BA.4-5 (5/5 micrograms/dose) should be used only for children 5 to 11 years of age. |
| **Pharmaceutical form and strengths** | **PBS-Sucrose (Comirnaty)**<br><br>*Individuals 12 years of age and older:*<br>30 micrograms/dose concentrate for dispersion for injection (Purple cap). After dilution each vial contains 6 doses of 0.3 mL |

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| | **Tris-sucrose (Comirnaty)**<br><br>*Individuals 12 years of age and older:*<br>30 micrograms/dose dispersion for injection (Grey cap):<br>One vial (2.25 mL) contains 6 doses of 0.3 mL.<br>The drug product does not require dilution for administration.<br><br>*Children 5 to 11 years:*<br>10 micrograms/dose concentrate for dispersion for injection (Orange cap).<br>After dilution each vial contains 10 doses of 0.2 mL.<br><br>*Infants and children 6 months to 4 years*<br>3 micrograms/dose concentrate for dispersion for injection (Maroon cap).<br>After dilution, each vial contains 10 doses of 0.2 mL.<br><br>**Tris-sucrose (Comirnaty Original/Omicron BA.1)**<br><br>*Individuals 12 years of age and older*<br>15/15 micrograms/dose dispersion for injection (Grey cap). One vial (2.25 mL) contains 6 doses of 0.3 mL.<br>The drug product does not require dilution for administration.<br><br>**Tris-sucrose (Comirnaty Original/Omicron BA.4-5)**<br><br>*Individuals 12 years of age and older*<br>15/15 micrograms/dose dispersion for injection (Grey cap). One vial (2.25 mL) contains 6 doses of 0.3 mL.<br>The drug product does not require dilution for administration.<br><br>*Children 5 to 11 years of age (i.e., 5 to less than 12 years of age)*<br>5/5 micrograms/dose concentrate for dispersion for injection (Orange cap).<br>After dilution each vial contains 10 doses of 0.2 mL. |
| **Is/will the product be subject to additional monitoring in the EU?** | Yes |

# PART II. SAFETY SPECIFICATION

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

### Indication

Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in:

- individuals 6 months of age and older (Comirnaty Original)
- individuals 12 years of age and older (Comirnaty Original/Omicron BA.1)
- individuals 5 years of age and older (Comirnaty Original/Omicron BA.4-5).

### Incidence:

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

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

As of 07 July 2022, the overall number of people who had been infected with SARS-CoV-2 was over 558 million worldwide,[4] an increase of 290 million since 05 April 2022.[5] Table 1 shows the incidence and prevalence as of 07 July 2022 for the US, UK, and EU-27 countries. In the EU and the UK, by 07 July 2022 the total number of confirmed cases had accumulated to 173 million people, or 33,679 per 100,000 people (from 148 million, or 28,895 per 100,000 by 05 April 2022). Across countries in the EU, the number of confirmed cases ranged from 15,422 to 51,870 cases per 100,000 people. Romania and Poland reported the lowest incidence rates while Slovenia, Portugal and Denmark reported the highest. [4]

In the US, the number of confirmed cases had reached nearly 90 million cases (26,849 per 100,000 people) by 07 July 2022.[4] This is an increase from over 81 million (24,482 per 100,000) by 05 April 2022.[5]

**Table 1. Incidence, Prevalence, and Mortality of COVID-19 as of 7 July 2022**

| | Total Cases | Incidence: Total Cases/ 100,000 | Active Cases | Prevalence: Active Cases/ 100,000 | Total Deaths | Mortality: Deaths / 100,000 | Population |
|---|---|---|---|---|---|---|---|
| Global | 514,171,689 | 6,460 | 39,074,357 | 491 | 6,263,821 | 79 | 7,959,019,177[a] |
| EU-27 | 150,353,573 | 33,729 | 7,175,315 | 1,610 | 1,104,404 | 248 | 445,774,395 |
| UK | 22,883,995 | 33,358 | 487,474 | 711 | 180,718 | 263 | 68,601,700 |
| EU-27 + UK | 173,237,568 | 33,679 | 7,662,789 | 1,490 | 1,285,122 | 250 | 514,376,095 |
| US | 89,930,463 | 26,849 | 3,376,945 | 1,008 | 1,044,557 | 312 | 334,950,275 |
| EU-27 Countries | | | | | | | |
| Austria | 4,499,646 | 49,395 | 116,641 | 1,280 | 18,825 | 207 | 9,109,533 |
| Belgium | 4,265,296 | 36,484 | 101,587 | 869 | 31,952 | 273 | 11,690,848 |
| Bulgaria | 1,175,725 | 17,180 | 26,574 | 388 | 37,263 | 544 | 6,843,529 |
| Croatia | 1,155,583 | 28,501 | 7,901 | 195 | 16,096 | 397 | 4,054,483 |
| Cyprus | 504,717 | 41,201 | 379,275 | 30,961 | 1,072 | 88 | 1,224,999 |
| Czech Republic | 3,937,630 | 36,633 | 7,148 | 67 | 40,325 | 375 | 10,748,849 |
| Denmark | 3,025,655 | 51,870 | 21,156 | 363 | 6,505 | 112 | 5,833,136 |
| Estonia | 581,457 | 43,774 | 55,937 | 4,211 | 2,599 | 196 | 1,328,325 |
| Finland | 1,158,485 | 20,844 | 43,846 | 789 | 4,941 | 89 | 5,557,992 |
| France | 31,813,342 | 48,523 | 1,784,489 | 2,722 | 149,854 | 229 | 65,563,357 |
| Germany | 28,808,614 | 34,165 | 1,607,287 | 1,906 | 141,627 | 168 | 84,321,573 |
| Greece | 3,792,674 | 36,747 | 185,065 | 1,793 | 30,400 | 295 | 10,320,919 |
| Hungary | 1,932,788 | 20,110 | 11,195 | 116 | 46,661 | 485 | 9,611,136 |
| Ireland | 1,600,614 | 31,705 | 33,243 | 658 | 7,467 | 148 | 5,048,493 |
| Italy | 19,157,174 | 31,779 | 1,198,697 | 1,988 | 168,864 | 280 | 60,283,442 |
| Latvia | 839,251 | 45,503 | 5,921 | 321 | 5,869 | 318 | 1,844,378 |
| Lithuania | 1,069,766 | 40,428 | 22,288 | 842 | 9,178 | 347 | 2,646,129 |
| Luxembourg | 263,167 | 40,712 | 10,824 | 1,674 | 1,094 | 169 | 646,419 |
| Malta | 107,306 | 24,173 | 8,337 | 1,878 | 753 | 170 | 443,903 |
| Netherlands | 8,224,378 | 47,786 | 129,063 | 750 | 22,401 | 130 | 17,210,955 |
| Poland | 6,019,633 | 15,940 | 567,483 | 1,503 | 116,449 | 308 | 37,763,440 |
| Portugal | 5,234,600 | 51,638 | 321,340 | NA | 24,273 | 239 | 10,137,059 |
| Romania | 2,927,187 | 15,422 | 11,700 | 62 | 65,755 | 346 | 18,980,269 |
| Slovakia | 1,799,054 | 32,920 | 5,683 | 104 | 20,154 | 369 | 5,464,949 |
| Slovenia | 1,046,425 | 50,321 | 12,877 | 619 | 6,657 | 320 | 2,079,511 |
| Spain | 12,890,002 | 27,548 | 486,757 | 1,040 | 108,259 | 231 | 46,791,117 |
| Sweden | 2,523,404 | 24,677 | 13,001 | 127 | 19,111 | 187 | 10,225,652 |

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

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. [6]

Further, as at-home rapid testing kits have become more readily available[7] 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.[8] Of all SARS-CoV-2 specimens sequenced by the CDC during the week ending 09

July 2022 Omicron BA.5 was identified in 65.0%, BA.2.12.1 was identified in 17.3%, BA.4 was identified in 16.3%, and BA.2 was identified in 1.4% specimens[8].

**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 07 July 2022, the overall prevalence estimates for the EU and UK were 1.610 and 711 active cases per 100,000, respectively, [4] compared to 2,967 and 12.819 active cases per 100,000 for both EU and UK respectively, on 15 April 2022[5]. The range of reported prevalence was 62 to 30,961 per 100,000: Romania, Slovakia and Czech Republic reported the lowest prevalence while France, Estonia, and Cyprus reported the highest (Table 1). It should be noted that Portugal, part of the EU-27, did not report active cases on 07 July 2022.

In the US, the prevalence on 07 July 2022 was 1,008 active cases per 100,000[4]. This is a decreased of approximately 3,483 per 100,000 since 05 April 2022, when the prevalence was 4,491 per 100,000[5].

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

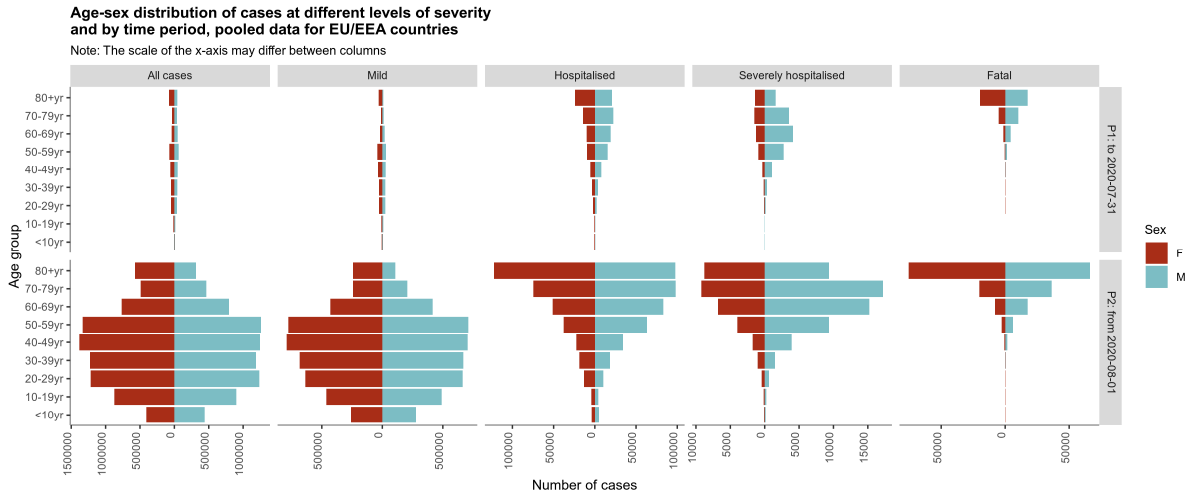
Since the beginning of the pandemic, the ECDC has continuously collected COVID-19 information from all EU/EEA member states. In the ECDC's TESSy database, COVID-19 case-based data, including age and gender, are available for over 80% of the official number of cases reported by ECDC epidemic intelligence,[9] 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 1.[10]

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

to COVID-19 cases overall. While age-sex patterns have remained consistent throughout the pandemic, a notable difference is that the absolute numbers of cases have increased dramatically in the latter period compared to the earlier one.

**Figure 1. Age-Sex distribution of COVID-19 Cases as Different Levels of Severity, Pooled data for EU/EEA countries. Case-based Data from TESSy produced on 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 COVID cases and deaths by age, sex, and race, as well as the cross-tabulation of age and sex, are shown in Table 2 as of 07 July 2022.[11]

At that time, the CDC reported that the US had recorded a total of 87,899,721 cases of COVID and 1,014,427 deaths attributable to the disease. However, because demographic data were not available for all US COVID cases and deaths, the numbers in Table 2 and Table 3 are drawn, respectively, from 79,688,152 cases and 869,882 deaths. Those under age 50 account for 70% of all cases but approximately for only 7% of deaths. Females account for a greater proportion of cases in all age groups except those ages 0-4 and those 5-11, however males account for a greater proportion of deaths in all age groups except for those ages 0-4 and 85+. Among the paediatric population, there is close to a 50-50 case distribution between males and females across ages 0-17. However, the paediatric mortality distribution is highly irregular between the sexes, with males being 49.8% of COVID deaths among 0-4-year-old, 59.1% among 5-11-year-old, 47.8% among 12-15-year-old, and 61.2% among 16-17-year-old.

**Table 2. Distribution of Cases (n=79,688,152) by Age, Sex, Race, and Cross-Tabulated Age and Sex -- United States as of 07 July 2022[a]**

| Event | Age Group | Age % | Sex | Sex % | Race[b] | Race % | Age Group | Females % | Males % | Other % |
|---|---|---|---|---|---|---|---|---|---|---|
| Cases | 0-4 | 3.3 | Females | 53.4 | H/L | 24.8 | 0-4 | 48.0 | 52.0 | <0.1 |
| | 5-11 | 6.7 | Males | 46.6 | AI/AN | 1.0 | 5-11 | 48.9 | 51.1 | <0.1 |
| | 12-15 | 4.7 | Other | <0.1 | Asian | 4.2 | 12-15 | 50.5 | 49.5 | <0.1 |
| | 16-17 | 2.7 | | | Black | 12.3 | 16-17 | 52.5 | 47.4 | <0.1 |
| | 18-29 | 21.1 | | | NH/PI | 0.3 | 18-29 | 54.8 | 45.2 | <0.1 |
| | 30-39 | 16.9 | | | White | 53.5 | 30-39 | 54.4 | 45.6 | <0.1 |
| | 40-49 | 14.3 | | | M/O | 4.0 | 40-49 | 54.3 | 45.7 | <0.1 |
| | 50-64 | 18.3 | | | | | 50-64 | 52.8 | 47.2 | <0.1 |
| | 65-74 | 6.8 | | | | | 65-74 | 52.2 | 47.8 | <0.1 |
| | 75-84 | 3.4 | | | | | 75-84 | 53.8 | 46.2 | <0.1 |
| | 85+ | 1.7 | | | | | 85+ | 63.4 | 36.6 | <0.1 |

a. Percentage of missing demographic data varied by types of event and demographic. Race/ethnicity available for 65% of cases, age available for 99% of cases, and sex available for 98% 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 3. Distribution of Deaths (n=869,882) by Age, Sex, Race, and Cross-Tabulated Age and Sex -- United States as of 07 July 2022[a]**

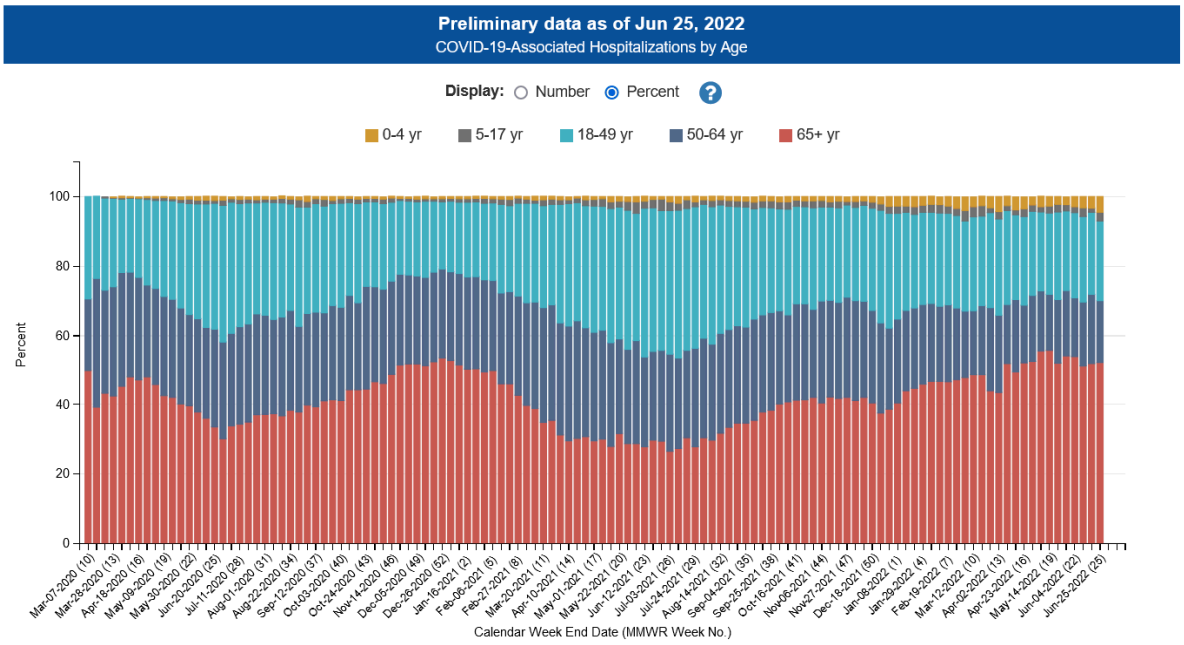
| Event | Age Group | Age % | Sex | Sex % | Race[b] | Race % | Age Group | Females % | Males % | Other % |
|---|---|---|---|---|---|---|---|---|---|---|
| Deaths | 0-4 | 0.1 | Females | 44.9 | H/L | 17.2 | 0-4 | 50.2 | 49.8 | <0.1 |
| | 5-11 | <0.1 | Males | 55.1 | AI/AN | 1.1 | 5-11 | 40.9 | 59.1 | <0.1 |
| | 12-15 | <0.1 | Other | <0.1 | Asian | 3.2 | 12-15 | 52.2 | 47.8 | <0.1 |
| | 16-17 | <0.1 | | | Black | 13.3 | 16-17 | 38.8 | 61.2 | <0.1 |
| | 18-29 | 0.7 | | | NH/PI | 0.2 | 18-29 | 40.1 | 59.9 | <0.1 |
| | 30-39 | 1.8 | | | White | 62.7 | 30-39 | 38.7 | 61.3 | <0.1 |
| | 40-49 | 4.1 | | | M/O | 2.2 | 40-49 | 37.4 | 62.6 | <0.1 |
| | 50-64 | 18.1 | | | | | 50-64 | 37.7 | 62.3 | <0.1 |
| | 65-74 | 22.6 | | | | | 65-74 | 40.5 | 59.5 | <0.1 |
| | 75-84 | 26 | | | | | 75-84 | 44 | 56 | <0.1 |
| | 85+ | 26.5 | | | | | 85+ | 56 | 44 | <0.1 |

a. Percentage of missing demographic data varied by types of event and demographic. Race/ethnicity available for 85% of deaths, age and sex available for 99% 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. As of July 2022, the network represents approximately 10% of the US population and covers 100 counties in the Emerging Infections Program (EIP) states and four other states.[12]

Based on data from COVID-NET, COVID-19 associated US hospitalizations, by age, for the period March 7, 2020, through June 25, 2022, are shown in Figure 2.[12] Persons aged 0-4 accounted for about 0-5% of admissions during that time period, while those aged 5-17, 8-49, 50-64 and 65+ years accounted for about 0-4%, 20-40%, 15-35% and 40-50%, respectively.

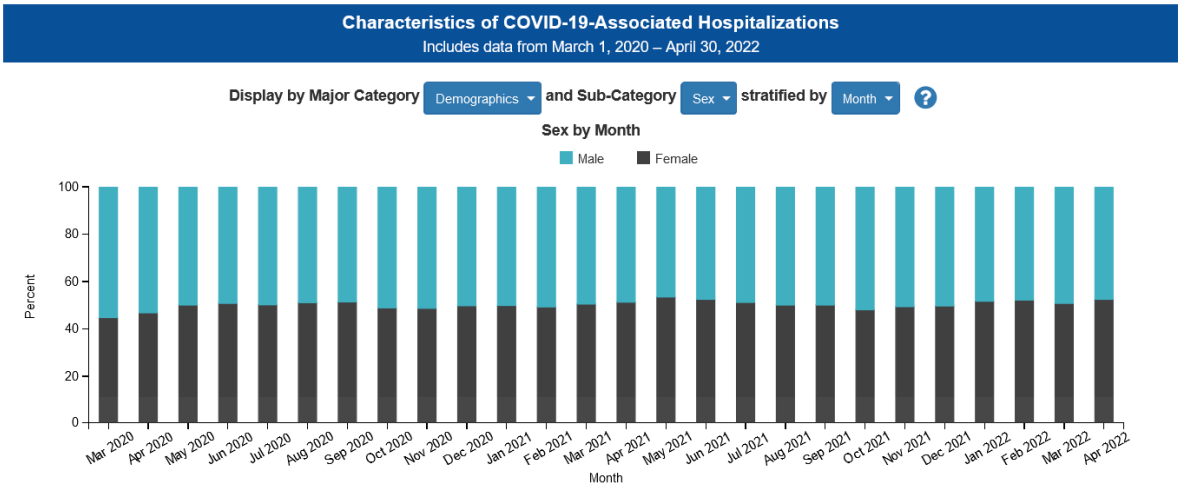
**Figure 2. COVID-19-Associated US Hospital Admissions by Age, March 2020 - June 2022**




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.

Based on data from COVID-NET, COVID-19 associated US hospitalizations, by sex, for the period March 2020, through April 2022, are shown in Figure 3.[13] For the most part, the distribution of patients hospitalized with COVID-19 has been about equal (± about 5%) between the sexes.

**Figure 3. COVID-19-Associated US Hospital Admissions by Sex, March 2020 - April 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, vaccination status, and discharge diagnoses are restricted to sampled and completed cases with non-missing data reported during March 1, 2020 – April 30, 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.
4. Vaccination status was obtained by matching hospitalized cases to state-based immunization information systems (IIS) data. Vaccination data are only available for 13 of 14 states. Unvaccinated cases have not received any vaccine doses per IIS data. Cases classified as "1st dose but < 14 days" tested positive for SARS-CoV-2 less than 14 days after receiving a single dose of vaccine. "Partially vaccinated" cases are those who tested positive for SARS-CoV-2 ≥14 days after receiving the first dose of a two-dose vaccination series through <14 days after the second dose in a two-dose series. "Fully vaccinated" cases tested positive for SARS-CoV-2 ≥14 days after either the second 2nd dose of a two-dose series or after one dose of a single-dose series. If SARS-CoV-2 test date was not available, date of admission was used to determine vaccination status. Data on vaccination, including data by age group, sex, and race/ethnicity, are only available from January 2021 onward.
Note that the proportion of hospitalized cases who are fully vaccinated is expected to increase as population vaccination coverage increases, especially in age groups with high vaccination coverage. The proportion of hospitalized cases who are fully vaccinated shown here are consistent with what we would expect in the setting of highly effective vaccines given current vaccination coverage in the population.

The demographic characteristics of persons infected with the Omicron variant of the COVID-19 virus may differ from that of persons infected with prior strains, although the data is not consistent across published studies.

As of January 20, 2022, Omicron had been identified in all EU/EEA countries.[14] 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.[14]

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).[15] 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 9 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.[16]

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).[17]

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.[18] 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.[19]

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.[20] 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.[21] 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.[22] 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.[23] 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.[24] [25] [26] [27] [28]

African American COVID-19 patients have been reported to have an increased risk of hospitalisation [25] [29] and mortality,[30] 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.[31] 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.

The most recent CDC estimate of the total number of excess deaths across the US from 01 February 2021 to 16 July 2022 from all causes (COVID 19 and otherwise) is 1,139,330.[32]

Figure 4 shows the weekly number of excess deaths in the US from January 2018 to June 2022, including and excluding deaths attributed to COVID-19 from the CDC. Weekly counts of deaths are compared with historical trends to determine whether the number of deaths is significantly higher than expected. In this analysis a model is used to generate a set of expected counts, and an upper bound threshold based on a one-sided 95% prediction interval of these expected counts is used to determine whether a significant increase in deaths has occurred. Estimates of excess deaths are provided based on the observed number of deaths relative to two different thresholds. The lower end of the excess death estimate range is generated by comparing the observed counts to the upper bound threshold, and a higher end of the excess death estimate range is generated by comparing the observed count to the average expected number of deaths.[33] Beginning around May of 2020 and continuing into 2022, the predicted number of all-cause deaths including COVID-19 deaths (blue bars), exceeded both of the thresholds. Per the CDC's methods, it should be noted that estimates of excess deaths reported may not be due to COVID-19.

**Figure 4. Weekly Deaths in the US Jan 2018 – June 2022 Including and Excluding COVID-19 Deaths[33]**

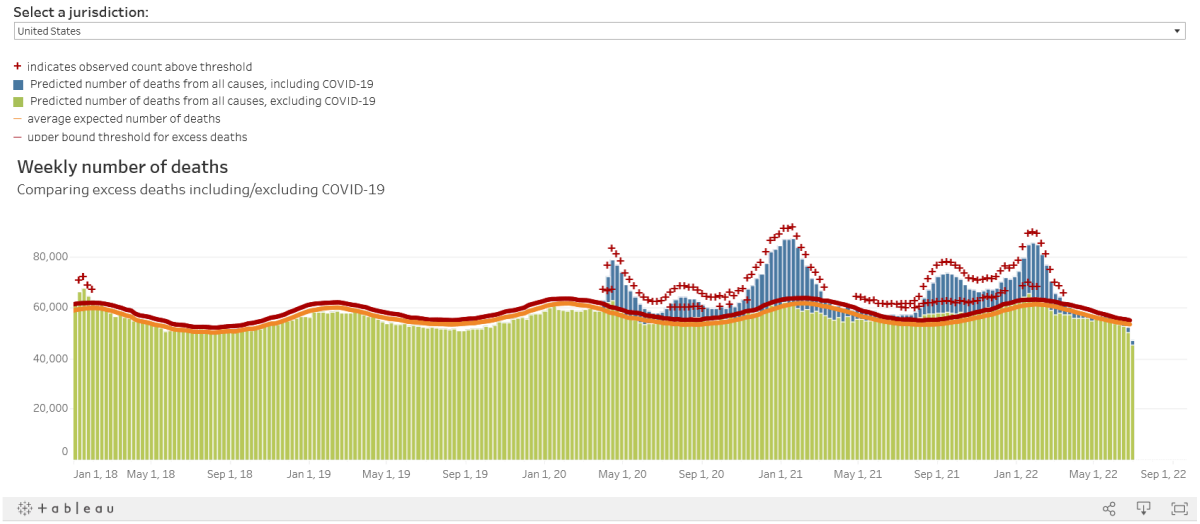


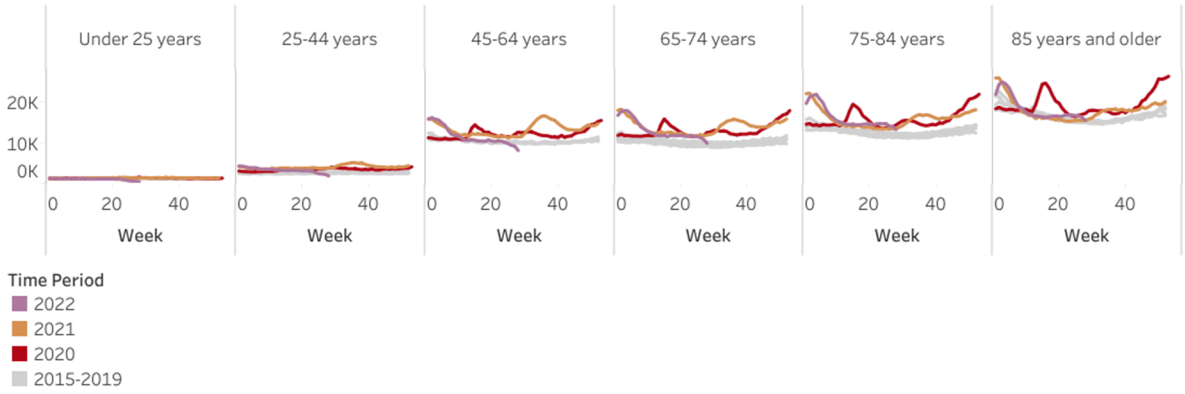

**Figure Notes:**

Number of deaths reported on this page are the total number of deaths received and coded as of the date of analysis and do not represent all deaths that occurred in that period. Data are incomplete because of the lag in time between when the death occurred and when the death certificate is completed, submitted to NCHS and processed for reporting purposes. This delay can range from 1 week to 8 weeks or more, depending on the jurisdiction and cause of death. See https://www.cdc.gov/nchs/nvss/vsrr/COVID19/index.htm for more information. Data for New York excludes New York City. Data on all deaths excluding COVID-19 exclude deaths with U07.1 as an underlying or multiple cause of death. Death counts were derived from the National Vital Statistics System database that provides the timeliest access to the vital statistics mortality data and may differ slightly from other sources due to differences in completeness, COVID-19 definitions used, data processing, and imputation of missing dates. Weighted estimates may be too high or too low in certain jurisdictions where the timeliness of provisional data has changed in recent weeks relative to prior years. Data for jurisdictions where counts are between 1 and 9 are suppressed.

An earlier CDC report on excess deaths covering 26 January 2020 through 03 October 2020 broke down excess deaths by demographics.[34] 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), and Native Americans and Native Alaskans (28.9% increase), all compared to an excess 11.9% deaths among non-Hispanic whites.

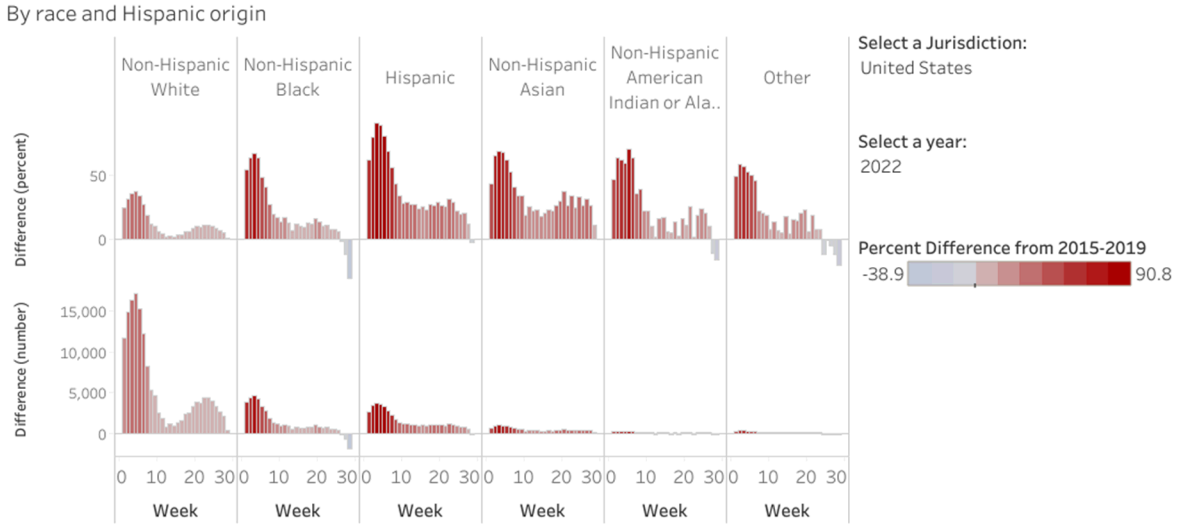
In a 2021 report, the CDC data on Excess Deaths Associated with COVID-19 reported that deaths in age groups 25-44, 45-64, 65-74, 85-84, and ≥ 85 years exceeded historical numbers from 2015-2019.[35] Figure 5 from the CDC provides a weekly count of deaths by age group in the US. Death rates were highest at the end of 2020 and into 2021 for all ages >45 years.

**Figure 5. Weekly counts of death by age group and by year**




Similarly, the number of deaths in 2022 by race and Hispanic origin increased above the historical average. At week 3, deaths among the Hispanic population increased 90.8% compared with the average from 2015-19. Likewise, by race, relative increases in deaths were seen across all groups that week: Asian Americans (+69.2%), African Americans (+67.5%), and Native Americans and Native Alaskans (+62.4%), and non-Hispanic whites (+35.5%)[33] Figure 6.

**Figure 6. Change in weekly number of deaths in 2021 compared to 2015-2019[33]**




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.[36] 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.[36]

For the period March 7, 2020 - June 25, 2022, the CDC's COVID-NET database recorded that 4,181 children aged 0-4 with a positive COVID test proximal to hospitalization and 4,808 children aged 5-17 with a positive COVID test proximal to hospitalization.[37]

Another recent CDC report described demographic trends in US COVID-19 incidence among 15,068 cases aged 0-24 years across 16 jurisdictions during the period 01 January 2020 through 31 December 2020.[38] The report broke down incidence by age groups and 2020 sub-periods that are presented in Table 4. The table shows that early in 2020, 5-9-year-old were experiencing less COVID-19 than 0-4-year-old, but by the end of the year this pattern had reversed. Compared to 5-9-year-old, the age categories 10-14, 15-19, and 20-24 years old showed progressively greater incidence rates, a pattern that held throughout 2020.

**Table 4. COVID-19 incidence and rate ratios, by age group among persons aged <25 years across three periods of 2020 in 16 U.S. jurisdictions [38]**

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

Other US paediatric data are generally consistent with the CDC findings. Table 5 summarizes demographic results for a retrospective cohort of 135,794 individuals under the age of 25 who were tested for COVID-19 by 08 September 2020 within the PEDSnet network of US paediatric health systems.[39] 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.

A study of 1,945,831 individuals aged 0-18 recorded in the Premier Healthcare Database between March and October 2020 included 20,714 paediatric cases of COVID-19; the authors reported similar patterns to what is shown in Table 4, with the additional observation

that COVID-19 cases aged 0-1 and 12-18 years were more likely to develop serious illness than those aged 2-11.[40]

**Table 5. Demographics of 135,794 US individuals under age 25 tested for COVID-19 by 08 September 2020[39]**

| | 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

## ***Risk Factors***

While anyone can become infected with SARS-CoV-2, COVID-19 disease can range from very mild (or no symptoms) to severe or fatal. A person's risk of initial infection increases through spending time in close physical proximity to others, especially in indoor spaces with poor ventilation.[41] 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.[41 42] Among children, the primary source of infection is an infected adult living in the same household.[43] According to the CDC, some ethnic minority groups have a higher risk of infection, but age is not associated with risk of initial infection among people aged 5 and older (Table 6).[44, 45]

**Table 6. Risk for COVID-19 Infection, Hospitalization, and Death in US by Age Group and by Race/Ethnicity**

| | | Rate ratios[a] | |
|---|---|---|---|
| **Age Group (years)** | **Cases[b]** | **Hospitalization[c]** | **Death[d]** |
| 0-4 | <1 | 1 | <1 |
| 5-17 | 1 | <1 | <1 |
| 18-29[e] | Ref | Ref | Ref |
| 30-39 | 1 | 2 | 4 |
| 40-49 | 1 | 2 | 10 |
| 50-64 | 1 | 3 | 25 |
| 65-74 | 1 | 5 | 60 |
| 75-84 | 1 | 8 | 140 |
| 85+ | 1 | 10 | 330 |
| Race/Ethnicity | | | |
| Non-Hispanic White[f] | Ref | Ref | Ref |
| American Indian or Alaska Native, non-Hispanic | 1.5 | 3.0 | 2.1 |
| Asian, non-Hispanic | 0.8 | 0.8 | 0.8 |
| Black or African American, non-Hispanic | 1.1 | 2.3 | 1.7 |
| Hispanic or Latino | 1.5 | 2.2 | 1.8 |

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 June 21, 2022, accessed on June 22, 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 March 1, 2020, through June 11, 2022, accessed on June 22, 2022). Rates were standardized to the 2000 US standard COVID-NET catchment population (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html).
d. Includes all deaths in National Center for Health Statistics (NCHS) provisional death counts (through May 28, 2022, accessed on June 22, 2022. The denominators used to calculate rates were based on the 2019 Vintage population (https://data.cdc.gov/NCHS/Provisional-COVID-19-Deaths-by-Sex-and-Age/9bhg-hcku).
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. Rate ratios for each race/ethnicity group are relative to the Non-Hispanic White category.

Risk for severe or fatal COVID-19 disease has been shown to increase with older age, male sex, or ethnic minority status. [44] [45] [46] [47] [48] [49] [50] Among adults, these risks increase for every 10-year age group above age 39. [44] [51] Table 6 also gives estimated rate ratios for COVID-19 hospitalisation and death by race/ethnicity relative to white, non-Hispanic persons in the US. The highest risk of hospitalization and death occurred in those who were American Indian or Alaska native persons (RR = 3.0 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.[45]

Children aged 5-17 typically experience a milder disease course and have lower risk of hospitalization or death.[45 49 51] 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. [52]

Risk of severe or fatal COVID-19 disease is higher among persons who are current or former smokers, have lower socioeconomic status, have no or public insurance, or live-in neighbourhoods with higher rates of limited English proficiency. [35 47] The CDC has also recognised other socio-demographic groups who may need to take extra precautions against COVID-19 due to increased risk for severe illness: pregnant women; breastfeeding mothers; people with disabilities; people with developmental, behavioural or substance abuse disorders; and newly resettled refugee populations.[53]

Among adults, risk for severe or fatal COVID-19 disease increases with the presence of chronic medical conditions, including obesity, chronic lung diseases (e.g., COPD or asthma), cardiovascular disease, diabetes, cancer, liver disease, neurological diseases (e.g., stroke or dementia), chronic kidney disease, sickle cell disease, immunosuppression, HIV higher scores on the WHO Clinical Progression Scale and Charlson Comorbidity Index.[46 47 47 51 54] Table 7 shows the estimated hazard ratios of COVID-19 mortality associated with these chronic conditions and socio-demographics from a cohort study of 17 million adults (with 17,000 COVID-19-related deaths) in England.

The presence of one or more underlying medical conditions also increases risk of severe or fatal disease among children aged 5-17. [55 56 57 58] In particular, childhood obesity has been consistently associated with two to three times the risk of severe disease or hospitalization.[55 59 60] 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.[49 57]

**Table 7. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death [51]**

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

**Table 7. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death [51]**

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

a. Classification by HbA1c is based on the most recent measurement within 15 months of baseline.
b. eGFR is measured in ml min−1 per 1.73 $m^2$ and derived from the most recent serum creatinine measurement.
c. Index of Multiple Deprivation (derived from the patient's postcode)
Models were adjusted for age using a four-knot cubic spline for age, except for estimation of age-group hazard ratios. Ref, reference group; 95% CI, 95% confidence interval.

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

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). [20] The study also found that age was not a risk factor for Omicron transmission, as attack rates were high across all ages.

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. Reinfections were defined as infection ≥90 days after 1st infection. [21] Having been vaccinated more than 120 days ago 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. 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.[22] 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 July 2022, 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[61] and received an emergency use authorization (EUA) in children 5 through 11 years of age on 29 October 2021.[62] Novavax Adjuvanted COVID-19 Vaccine received an EUA on 13 July 2022 for those 18 years of age and older. [63]

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 8).[63]

## Table 8. Drugs or Non-Vaccine Biologics with Emergency Use Authorization or Full Approval from the FDA

| Date of Issuance | Drug or Non-Vaccine Biologic | Note |
|---|---|---|
| 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 hospitalisation. |
| 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 8. Drugs or Non-Vaccine Biologics with Emergency Use Authorization or Full Approval from the FDA

| Date of Issuance | Drug or Non-Vaccine Biologic | Note |
|---|---|---|
| 5/26/2021 | Sotrovimab<br>(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)<br>(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):<br>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<br>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<br>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<br>(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. |

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

***Symptoms of COVID-19***

The clinical manifestations of COVID-19 vary widely from asymptomatic infection in 17- 45 %, across age groups[64 65 66 67] to critical illness and death. The rate of asymptomatic infection decreases with increasing age and long-term care facilities are associated with a lower rate of asymptomatic infection when compared to household transmission or other healthcare facilities.[67] One recent meta-analysis has estimated that 46.7% of infections in children are asymptomatic. [67] The most common symptoms of COVID-19 are fever, cough, and shortness of breath for both children and adults (Table 9).[68 69] Confirming these observations in a recent systematic review, researchers examined 1,140 cases of COVID-19 in children from 23 published studies. They reported that 11% of cases were asymptomatic. Among symptoms, fever was reported in 48%, cough 37%, any nasopharyngeal symptom 22%.[70]

**Table 9. Signs and Symptoms among 291 Paediatric (age <18 years) and 10,944 Adult (age 18–64 years) Patients[a] with laboratory confirmed COVID-19 — United States, February 12–April 2, 2020**

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

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

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%).[71] 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). [72] 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).[15]

***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.[73] [74] 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.[75] 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. [70] [73] [76]

***Progression and Timeline of Severe Disease Requiring Hospitalisation***

Those with severe disease will require hospitalisation to manage their illness. Based on data that have been systematically collected for the US by the CDC between 01 August 2020 and 12 July 2022, there were 4,947,473 new hospital admissions for patients who tested positive for COVID-19 in the US.[77] For the week ending 10 July 2022, 9.4 per 100 000 population (country range: 0.0 - 21.5) were hospitalised due to COVID-19 in 15 countries of the EU/EEA with available data.[78]

Between 01 August 2020 and 12 July 2022, the CDC reports 137,838 total hospital admissions for patients with confirmed COVID-19 in the US for those 0-17 years of age. [77]

Recent studies have been published to identify risk factors for hospitalization. A study conducted by the US CDC used 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.[22]

The Los Angeles County (LAC) Department of Public Health conducted 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. [79]

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%).[80] [81] [82] [83]

COVID-19 patients also commonly experience gustatory disorders (44%) and olfactory disorders (53%).[84] 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). [17] 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.[81] Approximately 17% to 40% of those hospitalised with COVID-19 experience severe symptoms necessitating intensive care [24] [29] [80] 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.[40] [80] More than 75% of patients hospitalised with COVID-19 require supplemental oxygen.[85]

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.[73] In 12 countries of the EU/EEA with available data, 0.7 per 100 000 population (country range: 0.2-1.2) were in the ICU due to COVID-19 for the week ending 10 July 2022.[78] 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.[65] 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.[86]

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. [17] 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. [22]

***Mortality***

As of 15 July 2022, there were 1,018,035 deaths reported in the US for all age groups among 88,932,947 cases (1.1% of cases).[87] As of the week ending on 10 July 2022, the mortality rate was 8.3 per million population (country range: 0.0 - 70.5) in the EU for the 30 countries reporting data. [78] As of 27 March 2022, the UK has seen 165,046 deaths from COVID-19 in all age groups among 20,848,913 cases (0.8% of cases).[88]

According to a 2020 meta-analysis of paediatric studies published through October 2020, the mortality for paediatric patients 0.1-2%.[23] [65] 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.[89]

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

As of 07 July 2022, the overall SARS-CoV-2 mortality for the EU + UK was 1,285,122 deaths, or 250 per 100,000 people. Reported mortality among EU countries and the UK ranged from 88 to 544 deaths per 100,000 (Table 1). Finland and Cyprus reported the lowest mortality; Croatia, Hungary, and Bulgaria reported the highest. [4]

In the US, as of 07 July 2022, the mortality was 1,044,557 deaths (312 per 100,000 people). Mortality in the US was higher than that of the UK (263 per 100,000).[4]

Overall reported mortality among hospitalised COVID-19 patients varies from 12.% to 26% in the EU, US and UK. [29,31,90,91] Mortality rates are declining over time, presumably due to an improved understanding of COVID-19 and its management.[92] 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). [22]

***Complications of COVID-19 and Long-COVID***

Complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney, and coagulation system.[24,27,93] 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.[94]

COVID-19 symptoms can persist weeks or months beyond the acute infection.[95,96] 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).[97]

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%).[98]

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.[99] [100]

Children who are infected with COVID-19 are at risk of subsequent multisystem inflammatory syndrome (MIS-C) and often develop a rash following resolution of COVID-19.[65] [101, 102] As of June 27, 2022 there were 8,639 cases of MIS-C reported to health departments in the United States with 70 deaths reported among those who met the MIS-C case definition.[103] Additional symptoms of MIS-C include abdominal pain, bloodshot eyes, chest tightness or pain, diarrhoea, lethargy, headache, low blood pressure, neck pain, and vomiting.[104] 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.[105] [106]

**Important co-morbidities:**

Important comorbidities in hospitalised COVID-19 patients include hypertension, diabetes, obesity, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease or asthma, chronic kidney disease, cancer, and chronic liver disease. [25,26,27] [79,82] [107] 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 10 using TESSy data posted on 12 August 2021[108] below.

**Table 10. Preconditions among COVID-19 Patients in EU/EEA, by Severity of Disease. Case-based Data from TESSy Reported 12 August 2021[107]**

| | 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 11 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.[35]

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 11. 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%)[39]. 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.[36] 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%).[36]

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.[109]

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, 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, other condition, or pregnancy). The prevalence of the individual comorbidities was not reported by the authors. [15] It is possible that the low rate of comorbidities in this study population is driven by the relatively low age of the patients studied.

## 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.[110] 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 $1.05 \times 10^6$ plaque forming units of SARS-CoV-2 (strain USA-WA1/2020), split equally between the intranasal and intratracheal routes.[111] 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 ALC-0159, distribute from the plasma to the liver. While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC-0159. Further studies indicated metabolism played a role in the elimination of ALC-0315. Biodistribution was assessed using luciferase expression as a surrogate reporter formulated like COVID-19 mRNA vaccine, with the identical lipid composition. After IM injection of the LNP-formulated RNA encoding luciferase in BALB/c mice, luciferase protein expression was demonstrated at the site of injection 6 hours post dose and expression decreased over time to almost reach background levels after 9 days. Luciferase was detected to a lesser extent in the liver; expression was present at 6 hours after injection and was not detected by 48 hours after injection. After IM administration of a radiolabelled LNP-mRNA formulation containing ALC-0315 and ALC-0159 to rats, the percent of administered dose was also greatest at the injection site. Outside of the injection site, total recovery of radioactivity was greatest in the liver and much lower in the spleen, with very little recovery in the adrenal glands and ovaries. The metabolism of ALC-0315 and ALC-0159 was evaluated in blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys, and humans.

The in vivo metabolism was examined in rat plasma, urine, faeces, and liver samples from the PK study. ALC-0315 and ALC-0159 are metabolised by hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

In GLP toxicity studies, two variants of the COVID-19 mRNA vaccine candidate were tested, designated "variant 8" and "variant 9" (V8 and V9, respectively). The variants differ only in their codon optimisation sequences which are designed to improve antigen expression, otherwise the amino acid sequences of the encoded antigens are identical. COVID-19 mRNA vaccine (V9) was evaluated clinically and submitted for application. Two GLP-compliant repeat-dose toxicity studies were performed in Wistar Han rats; one with each variant. Both studies were 17 days in duration with a 3-week recovery period. A DART study in Wistar Han rats has been completed. Safety pharmacology, genotoxicity and carcinogenicity studies have not been conducted, in accordance with the 2005 WHO vaccine guideline.[112]

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[113] 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.[114] 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 12. There was no evidence of vaccine-elicited disease enhancement.

## Table 12. Key Safety Findings and Relevance to Human Usage

| Key Safety findings from Nonclinical Studies[a] | Relevance to Human Usage |
|---|---|
| **Pharmacology** | |
| **NHP Challenge Model**<br>No evidence of vaccine-elicited disease enhancement. | Suggests low risk of vaccine-enhanced disease in humans; being investigated in CTs. |
| **Toxicity** | |
| **Injection site reactions:**<br>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:**<br>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.<br><br>Decreased reticulocytes have not been observed in humans treated with the LNP-siRNA pharmaceutical Onpattro[113], suggesting this finding in rats is a species-specific effect.<br><br>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**<br>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. [112] In addition, the components of the vaccine construct are lipids and RNA and are not expected to have carcinogenic or genotoxic potential.

## Module SIII. Clinical Trial Exposure

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

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

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

Phase 1 of Study C4591001 comprised dose-level–finding evaluations of the 2 selected vaccine candidates; multiple dose levels (some corresponding to those evaluated in Study BNT162-01) were evaluated. Study vaccine was administered using the same 2-dose schedule as in Study BNT162-01 (21 days apart). Dose levels were administered first to an 18- to 55-year age cohort, then to a 56- to 85-year age cohort.

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

- the reactogenicity profile for BNT162b2 was more favourable than BNT162b1 in both younger and older adults with similar immunogenicity results.
- in the NHP challenge study (VR-VTR-10671 – see Module SII), a trend toward earlier clearance of BNT162b2 was observed in the nose.

Phase 2 of the study C4591001 (for which enrolment has completed) comprised the evaluation of safety and immunogenicity data for the first 360 participants (180 from the active vaccine group and 180 from the placebo group, with each group divided between the younger and older age cohorts) entering the study after completion of Phase 1.

The Phase 3 part of the study C4591001 (which is ongoing) evaluates the efficacy and safety in all participants (including the first 360 participants from Phase 2). Phase 3 introduced enrolment of participants 16 to 17 years of age to be evaluated with the 18- to 55-year-old cohort, as well as enrolment of a 12- to 15-year-old cohort, and immunogenicity data from participants 12- to 15-year-old cohort 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. To date, most placebo subjects have been unblinded to receive active vaccine at or prior to 6 months after the second dose, therefore, a placebo group for comparison of safety data are only available for up to 6 months post Dose 2.

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

Analysis of 6-month post Dose-2 data was conducted on 16 years of age and older cohort reported on 13 March 2021. Clinical trial exposure tables are provided in Annex 7 (refer from Table 1 to Table 24).

A further efficacy analysis has been conducted on 12- to 15-year-old cohort participants reported by 13 March 2021 (refer to Annex 7, Table 1, Table 3, Table 9, Table 13, and Table 15).

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

The results for Study C4591001 Phase 3 participants 18 to 55 years of age who received the BNT162b2 booster are provided in Annex 7 (from Table 25 to Table 27).

Further evaluation for the paediatric population (5-<12 years of age) has been conducted in study C4591007 (see Annex 7 from Table 28 to Table 35).

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

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

The study design was modified (Amendment 6) to provide the necessary safety and immunogenicity data to support an EUA and future licensure of a booster (third) 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 booster (3rd) dose of BNT162b2 for participants aged 5 to <12 years of age by demographic characteristics is shown in Annex 7, (Table 36 and Table 37). In addition, exposure in special population for participants 5 to <12 years of age who received a booster (3rd) dose is shown in Annex 7 (Table 38).

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 Table 13 to Table 18. Exposure in special populations for participants aged 2 years to <5 years of age is shown in Table 19.

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 Table 20 to Table 24. 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 25 and Table 26.

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 Table 27 to Table 31. 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 32 andTable 33.

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 Table 34 to Table 38. 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 39 and Table 40.

*Evaluation of boosting dose(s)*

The present submission provides new 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).

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 41 to Table 46.

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 47 to Table 50.

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

- C4591005: A phase 1/2 study placebo-controlled, randomized, and observer-blind study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy Japanese adults.
  One hundred sixty participants were randomly assigned in a 3:1 ratio to study intervention (candidate vaccine: 120, placebo: 40).

- C4591015[3]: A phase 2/3 placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older. A total of 348 (209 in phase 2 and 139 in phase 3) pregnant women at 24 to 34 weeks gestation were randomised in a 1:1 ratio to vaccine or placebo.

- C4591020[4]: A phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of multiple formulations of the vaccine candidate BNT-162B2 against Covid-19 in healthy adults 18 through 55 years of age.

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

- C4591030[4]: A Phase 3, randomized, observer-blind trial to evaluate the safety and immunogenicity of BNT162b2 when coadministered with seasonal inactivated influenza vaccine (SIIV) in adults 18 through 64 years of age.

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

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

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

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

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

- BNT162-03:[5] Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b1) in Chinese healthy subjects: A phase I, randomized, placebo- controlled, observer-blind study.

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

- BNT162-06:[5] Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b2) in Chinese healthy population: A phase II, randomized, placebo-controlled, observer-blind study.

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

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

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

Population for analysis of CT data in this RMP includes the following 4 trials:

- 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.

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

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

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

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

*Exposure in participants 6 months to < 5 years (Study C4591007 Phase 1 - Cut-off date 16 July 2021)*

**Table 13. Exposure to BNT162b2 by Age Group and Dose (C4591007) – Phase 1 – 6 Months to <2 Years of Age – Open Label**

| Age Group<br>Dose<br>Exposure (Number of Doses Received) | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| 6 Months to <2 years | | |
| Vaccine 3 µg | | |
| 2 Doses | 16 | 32 |
| Total | 16 | 32 |

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**Table 14. Exposure to BNT162b2 by Age Group and Dose (C4591007) – Phase 1 – 2 to <5 Years of Age – Open Label**

| Age Group<br>Dose<br>Exposure (Number of Doses Received) | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| 2 years to <5 years | | |
| Vaccine 3 µg | | |
| 2 Doses | 16 | 32 |
| Total | 16 | 32 |
| Vaccine 10 µg | | |
| 2 Doses | 32 | 64 |
| Total | 32 | 64 |

PFIZER CONFIDENTIAL SDTM Creation: 09JAN2022 (12:50) Source Data: adsl Table Generation: 13JAN2022 (14:49) (Cutoff date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: (CDISC)/C4591007_6M_LT5Y_P1_RMP_PVP/adsl_s911_p1_5

**Table 15. Exposure to BNT162b2 by Age Group, Dose, and Gender (C4591007) – Phase 1 – 6 Months to <2 Years of Age – Open Label**

| | Number of Participants Exposed to BNT162b2 | | Total Number of Vaccine Doses | |
|---|---|---|---|---|
| **Age Group Dose** | **Male** | **Female** | **Male** | **Female** |
| 6 Months to <2 years | | | | |
| Vaccine 3 µg | 10 | 6 | 20 | 12 |
| Total | 10 | 6 | 20 | 12 |

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**Table 16. Exposure to BNT162b2 by Age Group, Dose, and Gender (C4591007) – Phase 1 – 2 to <5 Years of Age – Open Label**

| | Number of Participants Exposed to BNT162b2 | | Total Number of Vaccine Doses | |
|---|---|---|---|---|
| **Age Group Dose** | **Male** | **Female** | **Male** | **Female** |
| 2 years to <5 years | | | | |
| Vaccine 3 µg | 9 | 7 | 18 | 14 |
| Vaccine 10 µg | 19 | 13 | 38 | 26 |
| Total | 28 | 20 | 56 | 40 |

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**Table 17. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 1 – 6 Months to <2 Years of Age – Open Label**

| Age Group<br>Dose<br>Race/Ethnic Origin | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| Participants 6 months to <2 years | | |
| Vaccine 3 µg | | |
| Racial origin | | |
| White | 14 | 28 |
| Asian | 1 | 2 |
| Multiracial | 1 | 2 |
| Total | 16 | 32 |
| Ethnic origin | | |
| Hispanic/Latino | 3 | 6 |
| Non-Hispanic/non-Latino | 13 | 26 |
| Total | 16 | 32 |

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**Table 18. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 1 – 2 to <5 Years of Age – Open Label**

| Age Group<br>Dose<br>Race/Ethnic Origin | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| Participants 2 years to <5 years | | |
| **Vaccine 3 µg** | | |
| Racial origin | | |
| White | 12 | 24 |
| Asian | 1 | 2 |
| Multiracial | 2 | 4 |
| Not reported | 1 | 2 |
| Total | 16 | 32 |
| Ethnic origin | | |
| Non-Hispanic/non-Latino | 16 | 32 |
| Total | 16 | 32 |
| **Vaccine 10 µg** | | |
| Racial origin | | |
| White | 26 | 52 |
| Black or African American | 2 | 4 |
| Asian | 2 | 4 |

## Table 18. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 1 – 2 to <5 Years of Age – Open Label

| Age Group<br>Dose<br>Race/Ethnic Origin | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| American Indian or Alaska Native | 1 | 2 |
| Multiracial | 1 | 2 |
| Total | 32 | 64 |
| Ethnic origin | | |
| Hispanic/Latino | 1 | 2 |
| Non-Hispanic/non-Latino | 31 | 62 |
| Total | 32 | 64 |

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## Table 19. Exposure to BNT162b2 by Special Population (C4591007) – Phase 1 – 2 to <5 Years of Age – Open Label

| Population | Number of Participants Exposed to BNT162b2 (3 µg) (N[a]=16) n[b] | Number of Participants Exposed to BNT162b2 (10 µg) (Na=32) n[b] | Total Number of Vaccine Doses |
|---|---|---|---|
| Participants with any baseline comorbidity[c] | 0 | 2 | 4 |
| Blood disorders | 0 | 1 | 2 |
| Obese[d] | 0 | 1 | 2 |

Abbreviations: BMI = body mass index; 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.
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*Exposure in participants 6 months to < 5 years (Study C4591007 Phase 2/3 - Cut-off date 29 April 2022) Blinded Placebo-Controlled Follow-up Period*

**Table 20. Exposure to BNT162b2 by Age Group and Dose (C4591007) – Phase 2/3 – Blinded Placebo-Controlled Follow-up Period**

| Age Group<br>Dose<br>Exposure (Number of Doses Received) | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| 6 months to <2 years | | |
| **Vaccine 3 µg** | | |
| 1 Dose | 12 | 12 |
| 2 Doses | 780 | 1560 |
| 3 Doses | 386 | 1158 |
| Total | 1178 | 2730 |
| 2 years to <5 years | | |
| **Vaccine 3 µg** | | |
| 1 Dose | 16 | 16 |
| 2 Doses | 1213 | 2426 |
| 3 Doses | 606 | 1818 |
| Total | 1835 | 4260 |

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**Table 21. Exposure to BNT162b2 by Dose (C4591007) – Phase 2/3 – Blinded Placebo-Controlled Follow-up Period**

| Dose<br>Exposure (Number of Doses Received) | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| **Vaccine 3 µg** | | |
| 1 Dose | 28 | 28 |
| 2 Doses | 1993 | 3986 |
| 3 Doses | 992 | 2976 |
| Total | 3013 | 6990 |

PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 23MAY2022 (11:03) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s922

**Table 22. Exposure to BNT162b2 by Age Group, Dose, and Gender (C4591007) – Phase 2/3 – Blinded Placebo-Controlled Follow-up Period**

| | Number of Participants Exposed to BNT162b2 | | Total Number of Vaccine Doses | |
|---|---|---|---|---|
| **Age Group Dose** | **Male** | **Female** | **Male** | **Female** |
| 6 months to <2 years | | | | |
| Vaccine 3 µg | 589 | 589 | 1360 | 1370 |
| 2 years to <5 years | | | | |
| Vaccine 3 µg | 901 | 934 | 2084 | 2176 |

PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 21MAY2022 (21:20) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s932

**Table 23. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 2/3 – Blinded Placebo-Controlled Follow-up Period**

| **Age Group Dose Race/Ethnic Origin** | **Number of Participants Exposed to BNT162b2** | **Total Number of Vaccine Doses** |
|---|---|---|
| Participants 6 months to <2 years | | |
| **Vaccine 3 µg** | | |
| Racial origin | | |
| White | 922 | 2122 |
| Black or African American | 42 | 94 |
| Asian | 91 | 224 |
| American Indian or Alaska Native | 3 | 7 |
| Multiracial | 117 | 277 |
| Not reported | 3 | 6 |
| Total | 1178 | 2730 |
| Ethnic origin | | |
| Hispanic/Latino | 161 | 359 |
| Non-Hispanic/non-Latino | 1014 | 2363 |
| Not reported | 3 | 8 |
| Total | 1178 | 2730 |
| Participants 2 years to <5 years | | |
| **Vaccine 3 µg** | | |
| Racial origin | | |
| White | 1469 | 3380 |
| Black or African American | 94 | 215 |
| Asian | 127 | 318 |
| American Indian or Alaska Native | 3 | 6 |
| Native Hawaiian or other Pacific Islander | 2 | 5 |
| Multiracial | 131 | 314 |
| Not reported | 9 | 22 |

**Table 23. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 2/3 – Blinded Placebo-Controlled Follow-up Period**

| Age Group<br>Dose<br>Race/Ethnic Origin | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| Total | 1835 | 4260 |
| Ethnic origin | | |
| Hispanic/Latino | 264 | 602 |
| Non-Hispanic/non-Latino | 1568 | 3651 |
| Not reported | 3 | 7 |
| Total | 1835 | 4260 |

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**Table 24. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591007) – Phase 2/3 – Blinded Placebo-Controlled Follow-up Period**

| Dose<br>Race/Ethnic Origin | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| **Vaccine 3 µg** | | |
| Racial origin | | |
| White | 2391 | 5502 |
| Black or African American | 136 | 309 |
| Asian | 218 | 542 |
| American Indian or Alaska Native | 6 | 13 |
| Native Hawaiian or other Pacific Islander | 2 | 5 |
| Multiracial | 248 | 591 |
| Not reported | 12 | 28 |
| Total | 3013 | 6990 |
| Ethnic origin | | |
| Hispanic/Latino | 425 | 961 |
| Non-Hispanic/non-Latino | 2582 | 6014 |
| Not reported | 6 | 15 |
| Total | 3013 | 6990 |

PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 21MAY2022 (21:20) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s952

**Table 25. Exposure to BNT162b2 by Special Population (C4591007) – Phase 2/3 – 6 Months to <2 Years of Age – Blinded Placebo-Controlled Follow-up Period**

| Population | Number of Participants Exposed to BNT162b2 3 µg (Na=1178) n[b] | Total Number of Vaccine Doses |
|---|---|---|
| Participants with any baseline comorbidity[c] | 50 | 116 |
| Asthma | 10 | 22 |
| Blood disorders | 1 | 2 |
| Cardiovascular disease | 5 | 11 |
| Congenital heart disease | 10 | 24 |
| Chronic Lung Disease | 2 | 6 |
| Disabilities | 4 | 11 |
| Neurological disorder | 3 | 7 |
| Prematurity | 19 | 43 |

Abbreviations: 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.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (08:24) Source Data: admh Table Generation: 20MAY2022 (21:18) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/admh_s953_p2

**Table 26. Exposure to BNT162b2 by Special Population (C4591007) – Phase 2/3 – 2 to <5 Years of Age – Blinded Placebo-Controlled Follow-up Period**

| Population | Number of Participants Exposed to BNT162b2 3 µg (N[a]=1835) n[b] | Total Number of Vaccine Doses |
|---|---|---|
| Participants with any baseline comorbidity[c] | 222 | 511 |
| Asthma | 52 | 121 |
| Blood disorders | 1 | 3 |
| Cardiovascular disease | 5 | 11 |
| Chronic metabolic disease | 1 | 2 |
| Congenital heart disease | 12 | 28 |
| Feeding tube dependent | 4 | 9 |
| Immunocompromised condition | 1 | 3 |
| Obese[d] | 120 | 271 |
| Chronic Lung Disease | 5 | 9 |
| Disabilities | 17 | 40 |
| Neurological disorder | 11 | 27 |
| No CDC Category match | 2 | 5 |

**Table 26. Exposure to BNT162b2 by Special Population (C4591007) – Phase 2/3 – 2 to <5 Years of Age – Blinded Placebo-Controlled Follow-up Period**

| Population | Number of Participants Exposed to BNT162b2 3 µg (N[a]=1835) n[b] | Total Number of Vaccine Doses |
|---|---|---|
| Prematurity | 21 | 46 |

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; MMWR = Morbidity and Mortality Weekly Report.
a. N = number of participants in the specified group.
b. n = Number of participants with the specified characteristic. Participants with multiple occurrences within each category are counted only once.
c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥ 95th percentile).
d. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (08:24) Source Data: admh Table Generation: 20MAY2022 (21:18) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/admh_s953_p5

*Open-Label Follow-up Period – Participants who originally received Placebo and then received BNT162b2 after unblinding*

**Table 27. Exposure to BNT162b2 by Age Group and Dose (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

| Age Group<br>Dose<br>Exposure (Number of Doses Received) | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| 6 months to <2 years | | |
| **Vaccine 3 µg** | | |
| 1 Dose | 48 | 48 |
| 2 Doses | 219 | 438 |
| 3 Doses | 77 | 231 |
| Total | 344 | 717 |
| 2 years to <5 years | | |
| **Vaccine 3 µg** | | |
| 1 Dose | 23 | 23 |
| 2 Doses | 194 | 388 |
| 3 Doses | 89 | 267 |
| Total | 306 | 678 |
| **Vaccine 10 µg[a]** | | |
| 1 Dose | 14 | 14 |
| 2 Doses | 60 | 120 |
| 3 Doses | 2 | 6 |

**Table 27. Exposure to BNT162b2 by Age Group and Dose (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

| Age Group<br>Dose<br>Exposure (Number of Doses Received) | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| Total | 76 | 140 |

Note: Includes participants who became eligible for unblinding, confirmed to have received placebo originally and then received BNT162b2 post unblinding.
Note: Participants who received 2 different doses are counted once for each dose.
a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10µg.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 20MAY2022 (22:28) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s913

**Table 28. Exposure to BNT162b2 by Dose (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

| Dose<br>Exposure (Number of Doses Received) | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| **Vaccine 3 µg** | | |
| 1 Dose | 71 | 71 |
| 2 Doses | 413 | 826 |
| 3 Doses | 166 | 498 |
| Total | 650 | 1395 |
| **Vaccine 10 µg[a]** | | |
| 1 Dose | 14 | 14 |
| 2 Doses | 60 | 120 |
| 3 Doses | 2 | 6 |
| Total | 76 | 140 |

Note: Includes participants who became eligible for unblinding, confirmed to have received placebo originally and then received BNT162b2 post unblinding.
Note: Participants who received 2 different doses are counted once for each dose.
a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 23MAY2022 (11:03) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s923

**Table 29. Exposure to BNT162b2 by Age Group, Dose, and Gender (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

| | Number of Participants Exposed to BNT162b2 | | Total Number of Vaccine Doses | |
|---|---|---|---|---|
| **Age Group Dose** | **Male** | **Female** | **Male** | **Female** |
| 6 months to <2 years | | | | |
| **Vaccine 3 µg** | 166 | 178 | 354 | 363 |
| 2 years to <5 years | | | | |
| **Vaccine 3 µg** | 162 | 144 | 362 | 316 |
| **Vaccine 10 µg**[a] | 45 | 31 | 85 | 55 |
| Total | 201 | 169 | 447 | 371 |

Note: Includes participants who became eligible for unblinding, confirmed to have received placebo originally and then received BNT162b2 post unblinding.
Note: Participants who received 2 different doses are counted once for each dose
a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 21MAY2022 (21:20) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s933

**Table 30. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

| **Age Group Dose Race/Ethnic Origin** | **Number of Participants Exposed to BNT162b2** | **Total Number of Vaccine Doses** |
|---|---|---|
| Participants 6 months to <2 years | | |
| **Vaccine 3 µg** | | |
| Racial origin | | |
| White | 269 | 564 |
| Black or African American | 16 | 32 |
| Asian | 23 | 47 |
| Multiracial | 32 | 65 |
| Not reported | 4 | 9 |
| Total | 344 | 717 |
| Ethnic origin | | |
| Hispanic/Latino | 37 | 75 |
| Non-Hispanic/non-Latino | 304 | 636 |
| Not reported | 3 | 6 |
| Total | 344 | 717 |
| Participants 2 years to <5 years | | |
| **Vaccine 3 µg** | | |
| Racial origin | | |

**Table 30. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

| Age Group<br>Dose<br>Race/Ethnic Origin | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| White | 237 | 521 |
| Black or African American | 17 | 39 |
| Asian | 22 | 49 |
| Multiracial | 29 | 67 |
| Not reported | 1 | 2 |
| Total | 306 | 678 |
| Ethnic origin | | |
| Hispanic/Latino | 42 | 87 |
| Non-Hispanic/non-Latino | 264 | 591 |
| Total | 306 | 678 |
| **Vaccine 10 µg[a]** | | |
| Racial origin | | |
| White | 55 | 104 |
| Black or African American | 1 | 2 |
| Asian | 8 | 15 |
| Multiracial | 11 | 18 |
| Not reported | 1 | 1 |
| Total | 76 | 140 |
| Ethnic origin | | |
| Hispanic/Latino | 12 | 24 |
| Non-Hispanic/non-Latino | 64 | 116 |
| Total | 76 | 140 |

Note: Includes participants who became eligible for unblinding, confirmed to have received placebo originally and then received BNT162b2 post unblinding.
Note: Participants who received 2 different doses are counted once for each dose.
a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 21MAY2022 (21:20) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s943

**Table 31. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

| Dose<br>Race/Ethnic Origin | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| **Vaccine 3 µg** | | |
| Racial origin | | |
| White | 506 | 1085 |
| Black or African American | 33 | 71 |
| Asian | 45 | 96 |
| Multiracial | 61 | 132 |
| Not reported | 5 | 11 |
| Total | 650 | 1395 |
| Ethnic origin | | |
| Hispanic/Latino | 79 | 162 |
| Non-Hispanic/non-Latino | 568 | 1227 |
| Not reported | 3 | 6 |
| Total | 650 | 1395 |
| **Vaccine 10 µg[a]** | | |
| Racial origin | | |
| White | 55 | 104 |
| Black or African American | 1 | 2 |
| Asian | 8 | 15 |
| Multiracial | 11 | 18 |
| Not reported | 1 | 1 |
| Total | 76 | 140 |
| Ethnic origin | | |
| Hispanic/Latino | 12 | 24 |
| Non-Hispanic/non-Latino | 64 | 116 |
| Total | 76 | 140 |

Note: Includes participants who became eligible for unblinding, confirmed to have received placebo originally and then received BNT162b2 post unblinding.
Note: Participants who received 2 different doses are counted once for each dose.
a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 21MAY2022 (21:20) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s953

**Table 32. Exposure to BNT162b2 by Special Population (C4591007) – Phase 2/3 – 6 Months to <2 Years of Age – Open-Label Follow-up Period – Participants Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

| Population | Number of Participants Exposed to BNT162b2 3 µg (N[a]=344) n[b] | Total Number of Vaccine Doses |
|---|---|---|
| Participants with any baseline comorbidity[c] | 22 | 47 |
| Asthma | 2 | 3 |
| Cardiovascular disease | 1 | 2 |
| Congenital heart disease | 8 | 19 |
| Feeding tube dependent | 1 | 3 |
| Chronic Lung Disease | 2 | 5 |
| Disabilities | 1 | 2 |
| Neurological disorder | 1 | 2 |
| No CDC Category match | 2 | 5 |
| Prematurity | 8 | 16 |

Abbreviations: 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.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (08:24) Source Data: admh Table Generation: 20MAY2022 (21:18) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/admh_s953_open_p2

**Table 33. Exposure to BNT162b2 by Special Population (C4591007) – Phase 2/3 – 2 to <5 Years of Age – Open-Label Follow-up Period – Participants Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

| Population | Number of Participants Exposed to BNT162b2 3 µg (N[b]=305) n[c] | Number of Participants Exposed to BNT162b2 10 µg[a] (N[b]=65) n[c] | Total Number of Vaccine Doses |
|---|---|---|---|
| Participants with any baseline comorbidity[d] | 47 | 13 | 127 |
| Asthma | 15 | 5 | 42 |
| Cardiovascular disease | 3 | 1 | 10 |
| Congenital heart disease | 3 | 1 | 9 |
| Obesee | 14 | 5 | 37 |
| Chronic Lung Disease | 3 | 2 | 8 |

**Table 33. Exposure to BNT162b2 by Special Population (C4591007) – Phase 2/3 – 2 to <5 Years of Age – Open-Label Follow-up Period – Participants Who Originally Received Placebo and Then Received BNT162b2 After Unblinding**

| Population | Number of Participants Exposed to BNT162b2 3 µg (N[b]=305) n[c] | Number of Participants Exposed to BNT162b2 10 µg[a] (N[b]=65) n[c] | Total Number of Vaccine Doses |
|---|---|---|---|
| Disabilities | 4 | 1 | 9 |
| Mood Disorders | 1 | 0 | 2 |
| Neurological disorder | 2 | 0 | 4 |
| No CDC Category match | 3 | 0 | 7 |
| Prematurity | 5 | 2 | 16 |

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; MMWR = Morbidity and Mortality Weekly Report.
a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg.
b. N = number of participants in the specified group.
c. n = Number of participants with the specified characteristic. Participants with multiple occurrences within each category are counted only once.
d. 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).
e. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (08:24) Source Data: admh Table Generation: 23MAY2022 (11:21) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/admh_s953_open_p5

*Open-Label Follow-up Period – Participants who originally received BNT162b2*

**Table 34. Exposure to BNT162b2 by Age Group and Dose (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received BNT162b2**

| Age Group<br>Dose<br>Exposure (Number of Doses Received) | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| 6 months to <2 years | | |
| **Vaccine 3 µg** | | |
| 1 Dose | 373 | 373 |
| Total | 373 | 373 |
| 2 years to <5 years | | |
| **Vaccine 3 µg** | | |
| 1 Dose | 314 | 314 |
| Total | 314 | 314 |
| **Vaccine 10 µg[a]** | | |

## Table 34. Exposure to BNT162b2 by Age Group and Dose (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received BNT162b2

| Age Group<br>Dose<br>Exposure (Number of Doses Received) | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| 1 Dose | 120 | 120 |
| 2 Doses | 1 | 2 |
| Total | 121 | 122 |

Note: Includes participants who received 1 dose or 2 doses of BNT162b2 in the Blinded Placebo-Controlled Follow-up Period.
Note: Participants who received 2 different doses are counted once for each dose.
a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 23MAY2022 (11:03) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s914

## Table 35. Exposure to BNT162b2 by Dose (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received BNT162b2

| Dose<br>Exposure (Number of Doses Received) | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| **Vaccine 3 µg** | | |
| 1 Dose | 687 | 687 |
| Total | 687 | 687 |
| **Vaccine 10 µg[a]** | | |
| 1 Dose | 120 | 120 |
| 2 Doses | 1 | 2 |
| Total | 121 | 122 |

Note: Includes participants who received 1 dose or 2 doses of BNT162b2 in the Blinded Placebo-Controlled Follow-up Period.
Note: Participants who received 2 different doses are counted once for each dose.
a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 23MAY2022 (11:03) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s924

**Table 36. Exposure to BNT162b2 by Age Group, Dose, and Gender (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received BNT162b2**

| | Number of Participants Exposed to BNT162b2 | | Total Number of Vaccine Doses | |
|---|---|---|---|---|
| **Age Group Dose** | **Male** | **Female** | **Male** | **Female** |
| 6 months to <2 years | | | | |
| **Vaccine 3 µg** | 179 | 194 | 179 | 194 |
| 2 years to <5 years | | | | |
| **Vaccine 3 µg** | 143 | 171 | 143 | 171 |
| **Vaccine 10 µg**[a] | 66 | 55 | 66 | 56 |
| Total | 209 | 226 | 209 | 227 |

Note: Includes participants who received 1 dose or 2 doses of BNT162b2 in the Blinded Placebo-Controlled Follow-up Period.
Note: Participants who received 2 different doses are counted once for each dose.
a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 21MAY2022 (21:20) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s934

**Table 37. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received BNT162b2**

| **Age Group Dose Race/Ethnic Origin** | **Number of Participants Exposed to BNT162b2** | **Total Number of Vaccine Doses** |
|---|---|---|
| Participants 6 months to <2 years | | |
| **Vaccine 3 µg** | | |
| Racial origin | | |
| White | 266 | 266 |
| Black or African American | 22 | 22 |
| Asian | 35 | 35 |
| American Indian or Alaska Native | 2 | 2 |
| Multiracial | 46 | 46 |
| Not reported | 2 | 2 |
| Total | 373 | 373 |
| Ethnic origin | | |
| Hispanic/Latino | 53 | 53 |
| Non-Hispanic/non-Latino | 319 | 319 |
| Not reported | 1 | 1 |
| Total | 373 | 373 |
| Participants 2 years to <5 years | | |
| **Vaccine 3 µg** | | |
| Racial origin | | |

**Table 37. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received BNT162b2**

| Age Group<br>Dose<br>Race/Ethnic Origin | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| White | 232 | 232 |
| Black or African American | 25 | 25 |
| Asian | 22 | 22 |
| American Indian or Alaska Native | 1 | 1 |
| Native Hawaiian or other Pacific Islander | 1 | 1 |
| Multiracial | 32 | 32 |
| Not reported | 1 | 1 |
| Total | 314 | 314 |
| Ethnic origin | | |
| Hispanic/Latino | 43 | 43 |
| Non-Hispanic/non-Latino | 271 | 271 |
| Total | 314 | 314 |
| **Vaccine 10 µg[a]** | | |
| Racial origin | | |
| White | 89 | 89 |
| Black or African American | 9 | 9 |
| Asian | 9 | 9 |
| Multiracial | 12 | 13 |
| Not reported | 2 | 2 |
| Total | 121 | 122 |
| Ethnic origin | | |
| Hispanic/Latino | 16 | 16 |
| Non-Hispanic/non-Latino | 105 | 106 |
| Total | 121 | 122 |

Note: Includes participants who received 1 dose or 2 doses of BNT162b2 in the Blinded Placebo-Controlled Follow-up Period.
Note: Participants who received 2 different doses are counted once for each dose.a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 21MAY2022 (21:20) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s944

**Table 38. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591007) – Phase 2/3 – Open-Label Follow-up Period – Participants Who Originally Received BNT162b2**

| Dose<br>Race/Ethnic Origin | Number of Participants Exposed to BNT162b2 | Total Number of Vaccine Doses |
|---|---|---|
| **Vaccine 3 µg** | | |
| Racial origin | | |
| White | 498 | 498 |
| Black or African American | 47 | 47 |
| Asian | 57 | 57 |
| American Indian or Alaska Native | 3 | 3 |
| Native Hawaiian or other Pacific Islander | 1 | 1 |
| Multiracial | 78 | 78 |
| Not reported | 3 | 3 |
| Total | 687 | 687 |
| Ethnic origin | | |
| Hispanic/Latino | 96 | 96 |
| Non-Hispanic/non-Latino | 590 | 590 |
| Not reported | 1 | 1 |
| Total | 687 | 687 |
| **Vaccine 10 µg[a]** | | |
| Racial origin | | |
| White | 89 | 89 |
| Black or African American | 9 | 9 |
| Asian | 9 | 9 |
| Multiracial | 12 | 13 |
| Not reported | 2 | 2 |
| Total | 121 | 122 |
| Ethnic origin | | |
| Hispanic/Latino | 16 | 16 |
| Non-Hispanic/non-Latino | 105 | 106 |
| Total | 121 | 122 |

Note: Includes participants who received 1 dose or 2 doses of BNT162b2 in the Blinded Placebo-Controlled Follow-up Period.
Note: Participants who received 2 different doses are counted once for each dose.
a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adsl Table Generation: 21MAY2022 (21:20) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/adsl_s954

**Table 39. Exposure to BNT162b2 by Special Population (C4591007) – Phase 2/3 – 6 Months to <2 Years of Age – Open-Label Follow-up Period – Participants Who Originally Received BNT162b2**

| Population | Number of Participants Exposed to BNT162b2 3 µg (N[a]=373) n[b] | Total Number of Vaccine Doses |
|---|---|---|
| Participants with any baseline comorbidity[c] | 17 | 17 |
| Asthma | 2 | 2 |
| Blood disorders | 1 | 1 |
| Cardiovascular disease | 3 | 3 |
| Congenital heart disease | 4 | 4 |
| Disabilities | 1 | 1 |
| Prematurity | 7 | 7 |

Abbreviations: 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.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (08:24) Source Data: admh Table Generation: 20MAY2022 (21:18) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/admh_s953_xover_p2

**Table 40. Exposure to BNT162b2 by Special Population (C4591007) – Phase 2/3 – 2 to <5 Years of Age – Open-Label Follow-up Period – Participants Who Originally Received BNT162b2**

| Population | Number of Participants Exposed to BNT162b2 3 µg (N[b]=314) n[c] | Number of Participants Exposed to BNT162b2 10 µg[a] (N[b]=121) n[c] | Total Number of Vaccine Doses |
|---|---|---|---|
| Participants with any baseline comorbidity[d] | 37 | 18 | 55 |
| Asthma | 8 | 5 | 13 |
| Cardiovascular disease | 2 | 1 | 3 |
| Congenital heart disease | 0 | 2 | 2 |
| Obese[e] | 24 | 9 | 33 |
| Chronic Lung Disease | 1 | 0 | 1 |
| Disabilities | 0 | 2 | 2 |
| Neurological disorder | 3 | 0 | 3 |
| No CDC Category match | 1 | 0 | 1 |
| Prematurity | 6 | 1 | 7 |

**Table 40. Exposure to BNT162b2 by Special Population (C4591007) – Phase 2/3 – 2 to <5 Years of Age – Open-Label Follow-up Period – Participants Who Originally Received BNT162b2**

| Population | Number of Participants Exposed to BNT162b2 3 µg (N[b]=314) n[c] | Number of Participants Exposed to BNT162b2 10 µg[a] (N[b]=121) n[c] | Total Number of Vaccine Doses |
|---|---|---|---|

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; MMWR = Morbidity and Mortality Weekly Report.
a. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg.
b. N = number of participants in the specified group.
c. n = Number of participants with the specified characteristic. Participants with multiple occurrences within each category are counted only once.
d. 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).
e. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (08:24) Source Data: admh Table Generation: 23MAY2022 (11:21) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_DOSE3/admh_s953_xover_p5

*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 41. 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<br>Vaccine<br>30 µg<br>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.
PFIZER CONFIDENTIAL 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 42. 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.
PFIZER CONFIDENTIAL 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 43. 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<br>Age Group | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| Vaccine 30 µg<br>>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.
PFIZER CONFIDENTIAL 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 44. 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<br>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.
PFIZER CONFIDENTIAL 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 45. 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.
PFIZER CONFIDENTIAL 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 46. 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) (Na=325) n[b] | Number of Subjects Exposed to BNT162b2 OMI (30 µg) (Na=327) n[b] | Number of Subjects Exposed to BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) (Na=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.
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]).
PFIZER CONFIDENTIAL 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 47. 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<br>Vaccine 30 µg<br>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.
PFIZER CONFIDENTIAL 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 48. 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.
PFIZER CONFIDENTIAL 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 49. 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.
PFIZER CONFIDENTIAL 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 50. Exposure to Study Vaccine by Special Population (C4591031 Substudy D) – Cohort 2

| Population | Number of Subjects Exposed to BNT162b2 OMI (30 µg) (Na=315) n[b] | Number of Subjects Exposed to BNT162b2 (30 µg) (Na=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 subjects 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/m2 [≥16 Years of age]).
PFIZER CONFIDENTIAL 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

## 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.

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

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

- The participants enrolled in Substudy E and Substudy D were 18 years of age and older.

**Exclusion criteria**

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

**Previous vaccination with any coronavirus vaccine**

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

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

Rationale: Minimal potential clinical impact on the target population.

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

Reason for exclusion: Phase 1 excluded participants with a previous clinical or microbiological diagnosis of COVID-19 because these participants may have some

degree of protection from subsequent infection by SARS-CoV-2 and therefore would confound the pivotal efficacy endpoint.

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

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

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

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

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

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

Rationale: Participants with potential immunodeficient status were not specifically included in the study population. However, since the study population is intended to be as representative as possible of the vulnerable population to COVID-19 illness, sub-analyses of immunogenicity data in future studies may provide further understanding of immune responses in this population.

**Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study**

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

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

Rationale: No impact on the safety of the target population.

**Women who are pregnant or breastfeeding**

Reason for exclusion: To avoid use in a vulnerable population.

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

Rationale: Maternal vaccination with COVID 19 mRNA vaccine is being studied in C4591015 to explore unexpected negative consequences to the embryo or foetus.

**Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study**

Reason for exclusion: To avoid misleading results deriving from non-compliance to study procedures.

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

Rationale: Safety profile of COVID-19 mRNA vaccine is not expected to differ in these subjects when properly administered.

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

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

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

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

**Table 51. 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.<br><br>**Booster dose Participants >55 years of age**<br>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.<br>**Booster dose Participants ≥18 years to ≤55 years of age**<br>Through the cut-off date of 11 March 2022, there were no CT cases of pregnancy from C4591031 sub study D, cohort 2.<br><br>**Participants 6 months to <5 years of age**<br>Not applicable.<br>**Participants 5 to <12 years of age**<br>Through the cut-off date of 06 September 2021, there were no CT cases of pregnancy from study C4591007. |

## Table 51. Exposure of Special Populations included or not in Clinical Trial Development Programmes

| Type of special population | Exposure |
|---|---|
| | **Participants 12 to 15 years of age**<br>Through the cut-off date of 13 March 2021, there were no cases of pregnancies from Study C4591001.<br>**Participants 16 years of age and older**<br>Through the cut-off date of 13 March 2021, there were 50 cases (52 events) originating from Study C4591001, and all were unique pregnancies.<br>**Booster (3rd dose) Participants 16 years of age and older)**<br>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.<br>**Booster (3rd dose) Participants 5 to <12 years of age**<br>Through the cut-off date of 22 March 2022, there were no cases of pregnancy from study C4591007. |
| Breastfeeding women | Breastfeeding women were not initially included in the COVID-19 mRNA vaccine clinical development program.<br>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.<br><br>**Booster dose Participants >55 years of age**<br>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.<br>**Booster dose Participants ≥18 years to ≤55 years of age**<br>Through the cut-off date of 11 March 2022, there were no CT cases reporting breastfeeding from C4591031 sub study D, cohort 2.<br><br>**Participants 6 months to <5 years of age**<br>Not applicable.<br>**Participants 5 to <12 years of age**<br>Through the cut-off date of 06 September 2021, there were no cases indicative of exposure during breastfeeding from study C4591007.<br>**Participants 12 to 15 years of age**<br>Through the cut-off date of 13 March 2021, there were no CT cases indicative of exposure during breastfeeding from Study C4591001.<br>**Participants 16 years of age and older**<br>Through the cut-off date of 13 March 2021, there were no CT cases indicative of exposure during breastfeeding from Study C4591001.<br>**Booster (3rd dose) Participants 16 years of age and older**<br>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.<br>**Booster (3rd dose) Participants 5 to <12 years of age**<br>Not applicable. |
| Participants with relevant comorbidities: | Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease |

## Table 51. Exposure of Special Populations included or not in Clinical Trial Development Programmes

| Type of special population | Exposure |
|---|---|
| • Participants with hepatic impairment<br>• Participants with renal impairment<br>• Participants with cardiovascular disease<br>• Immunocompromised participants<br>• Participants with a disease severity different from inclusion criteria in CTs | 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/m2, 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.<br><br>**Booster dose Participants >55 years of age**<br>Please refer to the exposure of special populations in Table 46 from C4591031 sub study E.<br>**Booster dose Participants ≥18 years to ≤55 years of age**<br>Please refer to the exposure of special populations in Table 50 from C4591031 sub study D, cohort 2.<br><br>**Participants 6 months to <5 years of age**<br>Please refer to the exposure of special populations in Table 19, Table 25, Table 26, Table 32, Table 33, Table 39, Table 40.<br>**Participants 5 to < 12 years of age**<br>Please refer to the exposure of special populations in Annex 7.<br>**Participants 12 to 15 years of age**<br>Please refer to the exposure of special populations in Annex 7.<br>**Participants 16 years of age and older**<br>Please refer to the exposure of special populations in Annex 7.<br>**Booster (3rd dose) Participants (16 years of age and older)**<br>Please refer to the exposure of special populations in Annex 7.<br>**Booster (3rd dose) Participants (5 to <12 years of age)**<br>Please refer to the exposure of special populations in Annex 7. |
| 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.<br><br>The safety and efficacy of Comirnaty Original/Omicron BA.1 in children aged less than 12 years of age has not yet been established.<br><br>The safety and efficacy of Comirnaty Original/Omicron BA.4-5 in children aged less than 5 years of age has not yet been established.<br><br>**Participants 6 months to <5 years of age**<br>As of the cut-off date of 29 April 2022:<br><br>• 3013 participants in the blinded-placebo controlled follow-up period received the Pfizer-BioNTech COVID-19 vaccine (Table 21). |

## Table 51. Exposure of Special Populations included or not in Clinical Trial Development Programmes

| Type of special population | Exposure |
|---|---|
| | • 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 (Table 28).<br>• 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 (Table 35).<br><br>**Participants 5 to < 12 years of age**<br>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.<br>**Participants 12 to 15 years of age**<br>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.<br>**Participants 16 years of age and older**<br>Six hundred and seventy-one (671) paediatric participants 16 to 17 years of age received COVID-19 mRNA vaccine through the DLP of 13 March 2021 in study C4591001.<br>**Booster (3rd dose) Participants 5 <12 years of age**<br>At the cut-off date of 22 March 2022, a total of 401 participants in Phase 2/3 of study C4501007 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:<br>4590 participants in the blinded placebo-controlled follow-up period.<br>4237 participants in the open-label follow-up period after unblinding<br>Nineteen (19) participants 65 years of age and over were from study BNT162-01 study through the cut-off date of 23 October 2020.<br><br>**Booster dose Participants 65 years of age and older**<br>Please refer to the exposure Tables from C4591031 sub study E.<br>**Booster (3th dose) Participants 65 years of age and older**<br>Through the cut-off date of 17 June 2021, there were no elderly participants (≥65 years old) from Study C4591001 enrolled in the booster group. |

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

## Module SV. Post-Authorisation Experience

### SV.1. Post-Authorisation Exposure

It is not possible to determine with certainty the number of individuals who received COVID-19 mRNA vaccine since it was first authorised for emergency use on 01 December 2020.

Estimated worldwide shipped doses may serve as a reasonable indicator of subject exposure, considering that approximately 76% of the shipped doses were administered; this estimation is a weight average considering the proportion of doses administered out of those shipped upon review of data currently available for the EU-EEA[6] countries and the US[7].

With these caveats in mind, it is estimated that approximately 3,555,998,805 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 18 June 2022, corresponding to approximately 2,693,922,584 estimated administered doses.[8]

Overall, through 18 June 2022, a total of 229,269,400 paediatric Tris/Sucrose doses were shipped worldwide.

The estimated cumulative number of shipped and administered doses of BNT162b2 by region based on data provided in the shipment tracker (Order Book)[9] from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 18 June 2022, are summarised in Table 52.

[6] Approximately 73% of the doses shipped in the EU-EEA countries were administered; this proportion has been calculated considering, out of total number of vaccine doses distributed in the EU-EEA countries, the total number of vaccine doses administered as per report on https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab, as of 16 June 2022.

[7] Approximately 77% of the doses shipped in the US were administered; this proportion has been calculated considering, out of total number of vaccine doses distributed in the US, the total number of vaccine doses administered as per report on https://covid.cdc.gov/covid-data-tracker/#vaccinations, as of 17 June 2022.

[8] License Partner data are not included in the reported amount.

[9] 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.

**Table 52. Cumulative Estimated Shipped and Administered Doses of BNT162b2 by Region Worldwide**

| Region/Country | % of Doses | Total Number of Shipped Doses | Total Number of Administered Doses |
|---|---|---|---|
| **Europe** | 33.3 | 1184790735 | 873840606 |
| European Union (27) | 24.6 | 874223640 | 638183257 |
| European Economic Area Countries (3) | 0.4 | 12454785 | 9091993 |
| Switzerland | 0.3 | 10501650 | 7981254 |
| UK | 3.4 | 121752585 | 92531965 |
| Other Countries[a] | 3.6 | 126651915 | 96255455 |
| Commonwealth of Independent States[a] | 1.1 | 39206160 | 29796682 |
| **North America** | 14.7 | 523868135 | 402657330 |
| US | 12.7 | 451754755 | 347851161 |
| Canada | 2.0 | 72113380 | 54806169 |
| **Central and South America[b]** | 14.4 | 510365375 | 387877685 |
| **Asia** | 29.6 | 1051292420 | 812428536 |
| Japan | 7.6 | 268925940 | 217830011 |
| Other Countries[c] | 22.0 | 782366480 | 594598525 |
| **Oceania** | 2.3 | 81140220 | 61666567 |
| Australia/New Zealand | 2.3 | 80243250 | 60984870 |
| Other Countries[d] | 0.0 | 896970 | 681697 |
| **Africa[e]** | 5.8 | 204541920 | 155451859 |
| **Total** | 100.0 | 3555998805 | 2693922584 |

a. Includes the non-EU countries (Albania, Andorra, Bosnia, Kosovo, Montenegro, North Macedonia, Serbia, Turkey and Vatican City) and the Commonwealth of Independent States (Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Tajikistan, Ukraine and Uzbekistan).
b. Includes Antigua & Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts & Nevis, Saint Lucia, Saint Vincent & the Grenadine, Suriname, Trinidad & Tobago and Uruguay.
c. Includes Bahrain, Bangladesh, Bhutan, Brunei, Cambodia, Indonesia, Iraq, Israel, Jordan, Korea, Kuwait, Laos, Lebanon, Malaysia, Maldives, Mongolia, Nepal, Oman, Pakistan, Palestine, Philippines, Qatar, Saudi Arabia, Singapore, Sri Lanka, Thailand, Timor-Leste, United Arab Emirates and Vietnam.
d. Includes Fiji, Nauru, Samoa, Solomon Islands, Tonga, Tuvalu.
e. Includes Angola, Benin, Botswana, Burkina Faso, Cabo Verde, Cameroon, Central Africa Republic, Chad, Comoros, Congo, Djibouti, Democratic Republic of Congo, Egypt, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Ivory Coast, Kenya, Kiribati, Lesotho, Liberia, Libya, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Namibia, Niger, Nigeria, Rwanda, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, Tanzania, Togo, Tunisia, Uganda and Zambia.

Out of the cumulative estimated shipped and administered doses, 1,948,639,685 and 1,480,966,161 respectively, were shipped to ROW (Non-EEA countries, Canada, Central and South America, Asian countries [excluding Japan], Oceania and Africa).

Cumulative license partner (Fosun) data on the number of BNT162b2 doses administered in Hong Kong, Macau and Taiwan is provided in Table 53.

**Table 53. Cumulative Administered Doses of BNT162b2 – License Partner Data**

| Region/Country | Total Number of Administered Doses |
|---|---|
| Asia | 27314884 |
| Hong Kong[a,b] | 10314451 |
| Macau[c,d] | 256403 |
| Taiwan[c,e] | 16744030 |

a. Cumulative through 18 June 2022.
b. Conditional Authorisation under legislation 599K.
c. Special Import Permit.
d. Cumulative through 21 June 2022.
e. Cumulative through 21 June 2022.

## Cumulative Exposure Data (Health Authority Public Data)

Cumulative data about the number of COMIRNATY® doses administered are published for EEA, Japan, and US in the respective Health Authorities' websites; these data are provided in Table 54 through Table 57.

Table 54 displays the EEA published data with number of doses administered for each age group and by dose number.

**Table 54. EU/EEA – Cumulative Number of BNT162b2 Administered Doses by Age Group and Dose Number**

| Age Group | 1st Dose | 2nd Dose | Dose Unknown | 3rd Dose[a] | 4th Dose[b] |
|---|---|---|---|---|---|
| < 18 years[c] | 13636393 | 11718536 | 982 | 1885318 | 1839 |
| 0 – 4 years[d] | 6570 | 5512 | 0 | 123 | 0 |
| 5 – 9 years[e] | 2400265 | 1552704 | 101 | 1101 | 0 |
| 10 – 14 years[e] | 4509303 | 4075582 | 420 | 199566 | 107 |
| 15 – 17 years[f] | 3551465 | 3307482 | 704 | 410503 | 258 |
| 18 – 24 years[g] | 11371811 | 10563808 | 4035 | 5272098 | 13263 |
| 25 – 49 years[g] | 51444284 | 49059427 | 36983 | 25414999 | 112807 |
| 50 – 59 years[g] | 23719359 | 23084094 | 25646 | 14917699 | 115305 |
| 60 – 69 years[g] | 16347236 | 16155340 | 28333 | 16472372 | 508401 |
| 70 – 79 years[g] | 15638054 | 15485654 | 21790 | 15020989 | 843612 |
| ≥ 80 years[g] | 12162934 | 11939294 | 9463 | 10747352 | 935314 |
| Age Unknown[e] | 80136 | 65263 | 28 | 18179 | 59 |
| EEA – All[h] | 224378211 | 223231140 | 126250 | 151603079 | 9331517 |

a. Indicated as Dose Additional 1 in the ECDC webpage.
b. Indicated as Dose Additional 2 in the ECDC webpage.
c. Data from 19 countries.
d. Data from 13 countries.
e. Data from 17 countries.
f. Data from 18 countries.
g. Data from 27 countries.
h. Data from 30 countries.

Cumulative period up to 2022 week 24 (up to 19 June 2022) – Downloaded on 18 June 2022
https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea

Table 55 provides, as per EMEA/H/C/005735/MEA/002.10 (11th SMSR) commitment, the cumulative total number of administered Comirnaty dose 3 (Dose additional 1 in the ECDC webpage) in EU/EEA, per country, and by age group. The table also contains data about Dose 4 (reported as Dose Additional 2).

## Table 55. EU/EEA – Cumulative Number of BNT162b2 Administered 3rd and 4th Doses by Age Group and Country

| Age Group by Dose ® Countries | <18 years | | 18 - 24 years | | 25 – 49 years | | 50 – 59 years | | 60 – 69 years | | 70 – 79 years | | ≥80 years | | Age Unknown | | ALL | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Dose 3 | Dose 4 | Dose 3 | Dose 4 | Dose 3 | Dose 4 | Dose 3 | Dose 4 | Dose 3 | Dose 4 | Dose 3 | Dose 4 | Dose 3 | Dose 4 | Dose 3 | Dose 4 | Dose 3 | Dose 4 |
| AT | 149818 | 0 | 383699 | 0 | 1824532 | 0 | 1019240 | 0 | 850592 | 0 | 623022 | 0 | 444947 | 0 | | | 5146032 | 0 |
| BE | 217445 | 1397 | 555191 | 5714 | 2488143 | 43055 | 1306086 | 48807 | 1195270 | 65338 | 851861 | 78443 | 545700 | 159222 | 0 | 0 | 6942251 | 400579 |
| BG | 829 | 0 | 17099 | 0 | 178925 | 0 | 131340 | 0 | 194564 | 0 | 179688 | 0 | 55025 | 0 | 0 | 0 | 756641 | 0 |
| CY | | | 31491 | 7 | 197248 | 249 | 80079 | 280 | 79136 | 4576 | 61714 | 10237 | 29782 | 7704 | 0 | 0 | 479447 | 23053 |
| CZ | 64536 | 0 | 161043 | 0 | 1291474 | 0 | 717228 | 0 | 847562 | 0 | 806828 | 0 | 332451 | 0 | | | 4156586 | 0 |
| DE | | | | | | | | | | | | | | | | | 49731767 | 5235439 |
| DK | | | 307330 | 0 | 1167386 | 0 | 699366 | 0 | 625579 | 0 | 556738 | 0 | 283294 | 0 | | | 3639689 | 0 |
| EE | 4138 | 93 | 24080 | 888 | 150508 | 5234 | 78706 | 2627 | 88436 | 2604 | 70437 | 1617 | 44183 | 1240 | 29 | 0 | 456349 | 14210 |
| EL | 3553 | 3 | 340741 | 121 | 1965277 | 3965 | 1068942 | 7582 | 1021888 | 74550 | 825051 | 124918 | 569454 | 103558 | 0 | 0 | 5791353 | 314694 |
| ES | 32057 | 462 | 1023148 | 4138 | 7624682 | 42758 | 5275741 | 43739 | 4926491 | 44635 | 3728992 | 32368 | 2629889 | 13964 | 0 | 0 | 25208943 | 181602 |
| FI | 14406 | 0 | 138920 | 0 | 879444 | 0 | 526986 | 0 | 593869 | 0 | 529840 | 0 | 293322 | 0 | 0 | 0 | 2962381 | 0 |
| FR | 843623 | 2588 | 3552493 | 22873 | 13638089 | 102484 | 7004761 | 168825 | 6646559 | 448796 | 5174638 | 707112 | 3173427 | 888811 | 0 | 0 | 39185859 | 2338345 |
| HR | 989 | 0 | 18115 | 6 | 184374 | 72 | 153973 | 80 | 245689 | 220 | 202042 | 375 | 93999 | 740 | 17 | 0 | 898192 | 1493 |
| HU | 53637 | 32 | 192630 | 1757 | 1233409 | 24567 | 626328 | 20945 | 806512 | 82280 | 650482 | 118480 | 282857 | 51769 | 0 | 0 | 3791047 | 299799 |
| IE | 94888 | 67 | 225371 | 307 | 1121029 | 3452 | 529084 | 4380 | 453880 | 88757 | 339642 | 146411 | 180834 | 80664 | 7 | 0 | 2849840 | 323971 |
| IS | | | 27048 | 3 | 108751 | 87 | 39375 | 119 | 35091 | 316 | 23288 | 581 | 11973 | 3159 | 0 | 0 | 245303 | 4265 |
| IT | 1311889 | 0 | 2718431 | 0 | 12156326 | 0 | 7477957 | 0 | 6376845 | 0 | 5332414 | 0 | 4474910 | 0 | | | 38536883 | 0 |
| LI | | | 1189 | 0 | 5678 | 0 | 3767 | 0 | 3388 | 0 | 2800 | 0 | 1338 | 0 | | | 18160 | 0 |
| LT | 1508 | 0 | 55113 | 0 | 289113 | 0 | 154543 | 0 | 178306 | 0 | 136029 | 0 | 76310 | 0 | 3 | 0 | 889414 | 0 |
| LU | | | 25976 | 906 | 142820 | 2056 | 69656 | 1456 | 51839 | 1009 | 32283 | 375 | 22084 | 10006 | | | 344658 | 15808 |
| LV | 2346 | 1 | 30415 | 6 | 189279 | 20 | 90226 | 10 | 100272 | 20 | 75486 | 15 | 41919 | 9 | 0 | 0 | 527597 | 80 |
| MT | 226 | 11 | 26118 | 30 | 159816 | 463 | 52197 | 367 | 56607 | 7033 | 37911 | 17200 | 17796 | 11487 | 3 | 0 | 349450 | 36582 |
| NL | 27940 | 0 | | | | | | | | | | | | | | | 9266117 | 2081682 |
| NO | 0 | 0 | 215907 | 0 | 1000979 | 0 | 574971 | 0 | 523458 | 0 | 425389 | 0 | 213127 | 0 | | | 2953831 | 0 |
| PL | | | 496732 | 0 | 3735728 | 0 | 1923529 | 0 | 2824743 | 0 | 2008675 | 0 | 850156 | 0 | 19605 | 0 | 11839563 | 0 |
| PT | | | 377941 | 225 | 2093355 | 2150 | 1257166 | 2171 | 1237816 | 4028 | 994533 | 9632 | 657389 | 299802 | 36 | 165 | 6618200 | 318008 |
| RO | 13719 | 2 | 97364 | 66 | 618683 | 1098 | 346623 | 800 | 371174 | 1900 | 223183 | 2148 | 73778 | 927 | | | 1730805 | 6939 |
| SE | | | 309765 | 1126 | 1726197 | 15753 | 985476 | 18848 | 940600 | 373461 | 934431 | 706835 | 520569 | 428102 | | | 5417038 | 1544125 |
| SI | 1198 | 0 | 25237 | 0 | 157671 | 0 | 119298 | 0 | 152731 | 0 | 122890 | 0 | 69999 | 0 | | | 647826 | 0 |
| SK | | | 76362 | 366 | 532569 | 1694 | 261509 | 560 | 391338 | 692 | 278826 | 404 | 104807 | 150 | 0 | 0 | 1645411 | 3866 |

Table 56 below shows the cumulative number of BNT162b2 dose administered in Japan.

**Table 56. Japan - Cumulative Number of BNT162b2 Administered Doses**

| | Dose Number | | | |
|---|---|---|---|---|
| | 1st Dose | 2nd Dose | 3rd Dose | 4th Dose |
| General population[a] | 80859379 | 80268661 | 45024154 | 78384 |
| Elderly | 32248732 | 32160764 | 20349603 | 53808 |
| Child[c] (5 to < 12 years) | 1334886 | 1185593 | N/A | N/A |
| Medical workers[b] | 6378205 | 5709228 | N/A | N/A |
| All | 87237584 | 85977889 | 45024154 | 78384 |

a. Including elderly and children for all doses. Starting from the 3rd dose, also includes medical workers.
b. Vaccinations for medical workers (1st and 2nd dose) was completed as of 30 July 2021. From the 3rd dose, medical workers are included in the general population.
c. Booster dose in children 5 to < 12 years is not approved in Japan.
Source: Government's website where this data was downloaded: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html Download Date: June 20, 2022, 05:00 p.m. [JST]

Table 57 shows the cumulative number of BNT162b2 doses administered in the US.

**Table 57. US - Cumulative Number of BNT162b2 Administered Doses**

| Population | No. of Doses |
|---|---|
| All | 349460399 |
| Fully vaccinated (2 doses) | 127603112 |
| With a 1st booster dose | 58521335 |
| 1st Booster dose with BNT162b2 after primary series with BNT162b2 (Homologous Dose Schedule) | 49297112 |
| 1st Booster dose with BNT162b2 after primary series with Moderna (Heterologous Dose Schedule) | 3156484 |
| 1st Booster dose with BNT162b2 after primary series with J&J (Heterologous Dose Schedule) | 2024045 |
| 1st Booster dose with BNT162b2 after primary series with other COVID-19 vaccines (Heterologous Dose Schedule)[a] | 51232 |
| 1st Booster dose with BNT162b2 after primary series with unknown COVID-19 vaccines (Heterologous Dose Schedule) | 3992462 |
| | |
| With a 2nd booster dose | 8756788 |

a. Not BNT162b2, Moderna or J&J vaccine.

Source https://covid.cdc.gov/covid-data-tracker/#vaccinations, as of 18 June 2022.

### 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 58.

**Table 58. 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**

**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, diarrhea 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)[115]

- ACCESS protocol[116]
- US CDC (preliminary list of AESI for VAERS surveillance)[117]
- 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.

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

Risk-benefit impact

Although not observed or identified neither in clinical studies nor in the post-authorization experience with COVID-19 vaccines, there is a theoretical risk, mostly based on non-clinical betacoronavirus data, of VAED occurring either before the full vaccine regimen is administered or in vaccinees who have waning immunity over time. If VAED were to be identified as a true risk, depending on its incidence and severity, it may negatively impact the overall vaccine benefit risk assessment for certain individuals.

**Missing Information: Use in Pregnancy and while breast feeding**

Risk-benefit impact

The safety profile of the vaccine is not fully known in pregnant or breastfeeding women due to their initial exclusion from the pivotal clinical study however, post-marketing experience in pregnant women is available.[118] Additionally 2 clinical studies of the safety and immunogenicity of the COVID-19 vaccine in pregnant women are ongoing (C4591009 and C4591015); 1 non-interventional study (C4591011) to assess whether sub-cohorts of interest, such as pregnant women, experience increased risk of safety events of interest following

receipt of the COVID-19 vaccine is planned and another 2 non-interventional studies, C4591021 and C4591022, are ongoing.

It is important to obtain long term follow-up on women who were pregnant at or around the time of vaccination so that any potential negative consequences to the pregnancy can be assessed and weighed against the effects of maternal COVID-19 on the pregnancy.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.1 (15/15 mcg) and of Comirnaty Original/Omicron BA.4-5 (15/15 mcg) during pregnancy and breast feeding.

**Missing Information: Use in immunocompromised patients**

Risk-benefit impact

The safety profile of the vaccine is not known in immunocompromised individuals due to their exclusion from the pivotal clinical study. The efficacy of the vaccine may be lower in immunocompromised individuals, thus decreasing their protection from COVID-19. A non-interventional study [C4591024 (former Safety and immunogenicity in high-risk adults)] to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age is approved.

The efficacy of Comirnaty Original/Omicron BA.1 (15/15 mcg) and of Comirnaty Original/Omicron BA.4-5 (15/15 mcg) may be lower in immunocompromised individuals.

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

Risk-benefit impact

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

**Missing Information: Use in patients with autoimmune or inflammatory disorders**

Risk-benefit impact

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

**Missing Information: Interaction with other vaccines**

Risk-benefit impact

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

may affect the efficacy or safety of either vaccine have not been performed. One protocol study (C4591030 - *Co-administration study with seasonal influenza vaccine*) is completed.

**Missing Information: Long term safety data**

Risk-benefit impact

The long-term safety of COVID-19 mRNA vaccine is unknown at present, however further safety data are being collected in ongoing Study C4591001 for up to 2 years following administration of dose 2 of COVID-19 mRNA vaccine and 2 non-interventional studies (C4591036 and C4591038) are planned.

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

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.

## 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 59. 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.<br><br>**Participants 5 to < 12 years of age**<br>The MMWR[119] 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.<br>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. |

## Table 59. Myocarditis and Pericarditis[a]

**Participants 12 to 15 years of age**
As per MMWR[119] (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[120] 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[121], 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[122] 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)**
There was no information on booster dose incidence of myocarditis or pericarditis in the literature.

**Participants 16 years of age and older**
As per MMWR[119] (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.

## Table 59. Myocarditis and Pericarditis[a]

An HCO study from Israel[123] 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.[124] 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.[125] 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[126], 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-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).[127]

Two studies from Israel report incidence of myocarditis and pericarditis after booster dose. Aviram et al[128] 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[129] 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**

- *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*

## Table 59. Myocarditis and Pericarditis[a]

**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.

- *Booster Dose Participants 12 years of age and older*

**Data from the safety database (non-CT)**
Through 30 June 2022, 41 potentially relevant cases of Myocarditis and Pericarditis were identified among subjects who received a booster dose on a total of 4049 cases reporting the administration of a booster (4th) dose. In 3 of these 41 cases, the subjects developed both myocarditis and pericarditis.

**Myocarditis (14) and Myopericarditis (2)**
Overall event seriousness and outcome of these 16 cases are summarized below; the cases involved adults and elderly patients, there were no patients under 18 years of age.

| | **Total Events N = 16** |
|---|---|
| Serious events | 16 |
| Events with Criterion of Hospitalization | 7 |
| **Distribution of events by Outcome** | |
| Outcome: Death | 0 |
| Outcome: Resolved/Resolving | 3 |
| Outcome: Not resolved | 6 |
| Outcome: Resolved with sequelae | 0 |
| Outcome: Unknown | 7 |

**Pericarditis (28)**

Overall event seriousness and outcome of these 28 cases are summarized below; the cases involved adults and elderly patients, there were no patients under 18 years of age.

| | **Total Events N = 28** |
|---|---|
| Serious events | 28 |
| Events with Criterion of Hospitalization | 15 |
| **Distribution of events by Outcome** | |
| Outcome: Death | 0 |
| Outcome: Resolved/Resolving | 14 |
| Outcome: Not resolved | 4 |
| Outcome: Resolved with sequelae | 1 |
| Outcome: Unknown | 9 |

- *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.

**Data from the safety database (non-CT).**
Through 15 April 2022, on a total of 309 cases reporting the administration of the vaccine, there were 2 children who experienced pericarditis: in the first case a 2-year-old participant erroneously received a dose for adults (dose number unknown) and experienced serious pericarditis with non-serious chest pain and palpitations; all with outcome not resolved. Relevant medical history and concomitant medications were not reported.

## Table 59. Myocarditis and Pericarditis[a]

In the 2nd case, a 4-year-old female patient erroneously received a dose for adults (dose number 1) and experienced serious pericarditis with non-serious chest pain, Chest discomfort, and Dyspnoea all with outcome not resolved. The patient's relevant medical history and concomitant medications were not reported. There were no cases of myocarditis 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.

- *Booster (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.
**Data from the safety database (non-CT)**
Through 31 August 2022, there were 250 children 5 to <12 years of age[c] who received a booster (3rd) dose. Out of these 250 cases, 1 potentially relevant case was retrieved from the myocarditis and pericarditis search strategy. This case reported the serious PT Myocarditis; there were no cases reporting Pericarditis.
An 11-year-old male subject previously received an unknown primary series of COVID-19 vaccine; chest pain, dyspnoea and myocarditis occurred 3 days after Pfizer-BioNTech COVID Vaccine administration: the child was hospitalized on the same day and spontaneously recovered the day after.

- *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.

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

**Data from the safety database (CT)[b]**
Through 28 February 2022, no cases were retrieved reporting myocarditis and pericarditis in the participants who received a booster dose.
**Data from the safety database (non-CT)**
Through 28 February 2022, 20 potentially relevant cases of Myocarditis and Pericarditis were identified among subjects who received a booster dose. Of these cases, 19 cases reported myocarditis and 2 cases reported pericarditis (in 1 of these 21 cases, the subjects developed both myocarditis and pericarditis, unique number was 20 cases).

**Myocarditis (19 cases):** Overall event seriousness and outcome of these 19 cases are summarized below:

| | **Total Events N = 19** |
|---|---|
| Serious events | 19 |
| Events with Criterion of Hospitalization | 13 |
| **Distribution of events by Outcome** | |
| Outcome: Death | 0 |
| Outcome: Resolved/Resolving | 6 |
| Outcome: Not resolved | 8 |
| Outcome: Resolved with sequelae | 1 |
| Outcome: Unknown | 4 |

## Table 59. Myocarditis and Pericarditis[a]

**Pericarditis (2 cases):** Overall event seriousness and outcome of these 2 cases are summarized below:

| | **Total Events N = 2** |
|---|---|
| Serious events | 2 |
| Events with Criterion of Hospitalization | 1 |
| **Distribution of events by Outcome** | |
| Outcome: Death | 0 |
| Outcome: Resolved/Resolving | 1 |
| Outcome: Not resolved | 0 |
| Outcome: Resolved with sequelae | 0 |
| Outcome: Unknown | 1 |

- *Participants 16 years of age and older*

**Data from the CT dataset**
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.

- *Booster (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.
**Data from the safety database (non-CT)**
Through 28 February 2022, potentially relevant 1806 cases were identified among subjects who received a booster dose: of these 1806 cases, 1307 cases reported myocarditis and 1002 cases reported pericarditis and pleuropericarditis (in 503 of these 1806 cases, the subjects developed both myocarditis and pericarditis; in 2 of these 1806 cases, the subjects developed both pericarditis and pleuropericarditis, unique number was 1301 cases.

**Myocarditis (1307 cases):** Overall event seriousness and outcome of these 1307 cases are summarized below:

| | **Total Events N = 1307 (%)** |
|---|---|
| Serious events* | 1304 (99.8) |
| Events with Criterion of Hospitalization | 542 (41.5) |
| **Distribution of events by Outcome** | |
| Outcome: Death | 15 (1.1) |
| Outcome: Resolved/Resolving | 318 (24.3) |
| Outcome: Not resolved | 351 (26.9) |
| Outcome: Resolved with sequelae | 15 (1.1) |
| Outcome: Unknown/No data | 610 (46.7) |

## Table 59. Myocarditis and Pericarditis[a]

**Pericarditis (1002 cases)**
Reported relevant PTs: Pericarditis (995) and Pleuropericarditis (9). Overall event seriousness and outcome of these 1002 cases are summarized below:

| | **Total Events N = 1004 (%)** |
|---|---|
| Serious events | 1002 (99.8) |
| Events with Criterion of Hospitalization | 307 (30.6) |
| **Distribution of events by Outcome** | |
| Outcome: Death | 6 (0.6) |
| Outcome: Resolved/Resolving | 275 (27.4) |
| Outcome: Not resolved | 211 (21.0) |
| Outcome: Resolved with sequelae | 10 (1.0) |
| Outcome: Unknown | 503 (50.1) |

Conclusion: the MAH has updated the labels to include information about myocarditis and pericarditis following vaccine administration; a Direct Healthcare Professional Communication (DHPC) to address these findings was distributed. Surveillance will continue.

**Risk factors and risk groups**

Post-authorization reports have been received for more males than females, over a wide age range and following dose 1 and dose 2 of the vaccine. Evaluation by the 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.[130] Cardiac arrhythmias, cardiac arrest or death were not found significantly associated with the vaccine. [121,126] 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. **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: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

### Table 60. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)[a]

**Potential mechanisms, evidence source and strength of evidence**

This potential risk is theoretical because it has not been described in association with the COVID-19 mRNA vaccine or it has not been reported from any other late phase clinical trial of other human vaccine. Animal models of SARS-CoV-2 infection have not shown evidence of VAED after immunisation, whereas cellular immunopathology has been demonstrated after viral challenge in some animal models administered SARS-CoV-1 (murine, ferret and non-human primate models) or MERS-CoV (mice model) vaccines.[110,131] This potential risk has been included based on these animal data with these related betacoronaviruses.
Historically, disease enhancement in vaccinated children following infection with natural virus has been observed with an inactivated respiratory syncytial virus vaccine.[132]
Potential mechanisms of enhanced disease may include both T cell-mediated [an immunopathological response favouring T helper cell type 2 ($T_h2$) over T helper cell type 1 ($T_h1$)] and antibody-mediated immune responses (antibody responses with insufficient neutralizing activity leading to formation of immune complexes and activation of complement or allowing for Fc-mediated increase in viral entry to cells).[133]

**Characterisation of the risk**

- *Booster Dose Participants >55 years of age*

**Data from the CT dataset C4591031 Substudy E)**
There were no severe COVID-19 cases in this population at the cut-off date of 05 April 2022 (Sentinel cohort) and through 16 May 2022 (expanded cohort).

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

**Data from the CT dataset C4591031 Substudy D, cohort 2)**
There were no severe COVID-19 cases in this population at the cut-off date of 11 March 2022.

- *Booster Dose Participants 12 years of age and older*

**Data from the safety database (non-CT)**
Through 30 June 2022, 32 relevant cases of potential VAED-VAERD were identified among subjects who received a booster dose on a total of 4049 cases reporting the administration of a booster (4th) dose.

Overall event seriousness and outcome of these 32 cases are summarized below:

| | Total Events N = 77 (%) |
|---|---|
| Serious events | 64 (83.1) |
| Events with Criterion of Hospitalization | 45 (58.4) |
| **Distribution of events by Outcome** | |
| Outcome: Death | 5 (6.5) |
| Outcome: Resolved/Resolving | 35 (45.5) |
| Outcome: Not resolved | 9 (11.7) |
| Outcome: Resolved with sequelae | 0 |
| Outcome: Unknown | 28 (36.4) |

The most frequently (≥2%) reported relevant PTs were Vaccination failure (19), COVID-19 pneumonia (16), Drug ineffective (13), Dyspnoea (10), Diarrhoea (4), Tachypnoea (3), Acute respiratory distress syndrome, Seizure, and Vomiting (2 each).

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

**Data from the CT database (study C4591007)**

**Table 61. Confirmed Case of Postvaccination Severe COVID-19 (Protocol or CDC-Defined) – Blinded and Open-label Follow-up Period (Prior to Crossover) – Phase 2/3 – 6 Months to <2 Years of Age – Safety Population (C4591007)**

| | BNT162b2 (3 µg) (N[a]=1178) | | Placebo (N[a]=598) | |
|---|---|---|---|---|
| **Timing** | **n[b] (%)** | **(95% CI[c])** | **n[b] (%)** | **(95% CI[c])** |
| PD1 Before Dose 2 | 0 | (0.0, 0.3) | 0 | (0.0, 0.6) |
| Within 7 days PD1 | 0 | (0.0, 0.3) | 0 | (0.0, 0.6) |
| PD2 Before Dose 3 | 0 | (0.0, 0.3) | 0 | (0.0, 0.6) |
| Within 7 days PD2 | 0 | (0.0, 0.3) | 0 | (0.0, 0.6) |
| PD3 Before Crossover Dose 1 | 0 | (0.0, 0.3) | 1 (0.2) | (0.0, 0.9) |
| Within 7 days PD3 | 0 | (0.0, 0.3) | 0 | (0.0, 0.6) |
| Total[d] | 0 | (0.0, 0.3) | 1 (0.2) | (0.0, 0.9) |

Abbreviations: PD1 = post-dose 1; PD2 = post-dose 2; PD3 = post-dose 3.
Note: This table includes participants only from Phase 2/3.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Total is the sum of PD1, PD2 and PD3.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adc19eu Table Generation: 24MAY2022 (14:38) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_D3_EFF/adeff_s901_eu_2

**Table 62. Confirmed Case of Postvaccination Severe COVID-19 (Protocol or CDC-Defined) – Blinded and Open-label Follow-up Period (Prior to Crossover) – Phase 2/3 – 2 to <5 Years of Age – Safety Population (C4591007)**

| | BNT162b2 (3 µg) (N[a]=1835) | | Placebo (N[a]=915) | |
|---|---|---|---|---|
| **Timing** | **n[b] (%)** | **(95% CI[c])** | **n[b] (%)** | **(95% CI[c])** |
| PD1 Before Dose 2 | 0 | (0.0, 0.2) | 0 | (0.0, 0.4) |
| Within 7 days PD1 | 0 | (0.0, 0.2) | 0 | (0.0, 0.4) |
| PD2 Before Dose 3 | 6 (0.3) | (0.1, 0.7) | 1 (0.1) | (0.0, 0.6) |
| Within 7 days PD2 | 0 | (0.0, 0.2) | 0 | (0.0, 0.4) |
| PD3 Before Crossover Dose 1 | 0 | (0.0, 0.2) | 0 | (0.0, 0.4) |
| Within 7 days PD3 | 0 | (0.0, 0.2) | 0 | (0.0, 0.4) |
| Total[d] | 6 (0.3) | (0.1, 0.7) | 1 (0.1) | (0.0, 0.6) |

Abbreviations: PD1 = post-dose 1; PD2 = post-dose 2; PD3 = post-dose 3.
Note: This table includes participants only from Phase 2/3.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.

**Table 60. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)[a]**

b. n = Number of participants reporting at least 1 occurrence of the specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Total is the sum of PD1, PD2 and PD3.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adc19eu Table Generation: 24MAY2022 (14:38) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_D3_EFF/adeff_s901_eu_5

**Table 63. Confirmed Case of Postvaccination Severe COVID-19 (CDC-Defined) – Blinded and Open-label Follow-up Period (Prior to Crossover) – Phase 2/3 – 2 to <5 Years of Age – Safety Population (C4591007)**

| | BNT162b2 (3 µg) (N[a]=1835) | | Placebo (N[a]=915) | |
|---|---|---|---|---|
| **Timing** | **n[b] (%)** | **(95% CI[c])** | **n[b] (%)** | **(95% CI[c])** |
| PD1 Before Dose 2 | 0 | (0.0, 0.2) | 0 | (0.0, 0.4) |
| Within 7 days PD1 | 0 | (0.0, 0.2) | 0 | (0.0, 0.4) |
| PD2 Before Dose 3 | 1 (0.1) | (0.0, 0.3) | 0 | (0.0, 0.4) |
| Within 7 days PD2 | 0 | (0.0, 0.2) | 0 | (0.0, 0.4) |
| PD3 Before Crossover Dose 1 | 0 | (0.0, 0.2) | 0 | (0.0, 0.4) |
| Within 7 days PD3 | 0 | (0.0, 0.2) | 0 | (0.0, 0.4) |
| Total[d] | 1 (0.1) | (0.0, 0.3) | 0 | (0.0, 0.4) |

Abbreviations: PD1 = post-dose 1; PD2 = post-dose 2; PD3 = post-dose 3.
Note: This table includes participants only from Phase 2/3.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Total is the sum of PD1, PD2 and PD3.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (06:32) Source Data: adc19eu Table Generation: 24MAY2022 (13:00) (Cutoff date: 29APR2022, Snapshot Date: 11MAY2022) Output File: (CDISC)/C4591007_6MLT5_P23_RMP_PVP_D3_EFF/adeff_s901_eu_cdc_5

Severe COVID-19 criteria (as described in the protocol, based on FDA definition) were fulfilled for 7 cases among children 2 to <5 years of age, of which 5/6 cases in the BNT162b2 group fulfilled a single criterion of increased heart rate or respiratory rate and 1 case in the placebo group fulfilled a single criterion of decreased SpO2 (88% on room air); these were all considered by the investigator as not clinically significant. The remaining case in the BNT162b2 group involved a child hospitalized for hypoxemia (88% on room air) and increased heart and respiratory rates who had coinfection with parainfluenza. Among children 6 months to <2 years of age, 1 case in the placebo group fulfilled a single criterion of increased heart rate (172 bpm) and

involved coinfection with enterovirus; no BNT162b2 group cases fulfilled any severe criteria. No MIS-C cases were reported in either age group.

There were no cases severe COVID-19 cases reported after Phase 2/3 Placebo Crossover Participants from 6 Months to <5 Years of Age.

**Data from the safety database (non-CT):**

Through 15 April 2022, there were no cases reporting VAED including VAERD in the safety database involving individuals 6 months to <5 years of age.

- *Participants 5 to <12 years of age*

**Data from the CT database (study C4591007)**
VAED including VAERD were not observed through the cut-off date of 06 September 2021.

- *Booster (3rd) dose in participants 5 to <12 years of age*

**Data from the CT database (study C4591007)**
Through 22 March 2022, there are no efficacy data on children 5 to <12 years of age 1 month after booster dose.
**Data from the safety database (non-CT)**
Through 31 August 2022, there were 250 children 5 to <12 years[c] of age who received a booster (3rd) dose. No cases of VAED/VAERD were retrieved in this dataset.

- *Participants 12 to 15 years of age*

**Data from the CT database[b]**
There were no cases reporting VAED/VAERD as SAEs in the CT dataset through the DLP of 30 September 2021.

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

**Data from the safety database (CT)**
Through 28 February 2022, there were no cases reporting VAED/VAERD as SAEs in the CT dataset.
**Data from the safety database (non-CT)[b]:**
Through 28 February 2022, no AE was reported that suggested any potential case of severe COVID 19 among individuals who received the booster dose.

- *Participants 16 years of age and older*

**Data from the CT database:[b]**
There were no cases indicative of VAED/VAERD as SAEs in the CT dataset through the DLP of 30 September 2021.

- *Booster (3rd) Dose Participants 16 years of age and older*

**Data from the CT database (Study C4591001)**
Through 17 June 2021, no AE were reported that suggested any potential case of severe COVID-19 among participants who received the booster dose.
**Data from the safety database (non-CT)**
Through 28 February 2022, 282 cases reporting 679 potentially relevant events were identified among subjects who received a booster dose.
The reported relevant PTs (≥ 20 occurrences) were: Vaccination failure (148), Drug ineffective (133), COVID 19 pneumonia (129), Dyspnoea (67), Diarrhoea (37), Myocarditis and Vomiting (20 each).
Seriousness criteria for the total 282 cases: Medically significant (92, of which 6 also serious for disability), Hospitalization required (non-fatal/non-life threatening) (122), Life threatening (17), and Death (51).

## Table 60. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)[a]

Overall event seriousness and outcome of these 282 cases are summarized below:

| | Total Events N = 679 (5%) |
|---|---|
| Serious events | 608 (89.5%) |
| Events with Criterion of Hospitalization | 379 (55.8%) |
| **Distribution of events by Outcome** | |
| Outcome: Death | 117 (17.2%) |
| Outcome: Resolved/Resolving | 203 (29.9%) |
| Outcome: Not resolved | 146 (21.5%) |
| Outcome: Resolved with sequelae | 4 (0.6%) |
| Outcome: Unknown/No data | 210 (30.9%) |

Conclusion:
The review of subjects with COVID-19 following vaccination, based on the current evidence, VAED/VAERD may remain a theoretical risk for the vaccine. Surveillance will continue.

**Risk factors and risk groups**

It is postulated that the potential risk may be increased in individuals producing lower neutralizing antibody titers or in those demonstrating waning immunity. [133]

**Preventability**

An effective vaccine against COVID-19 that produces high neutralizing titers and a $T_H1$ predominant $CD4^+$ T cell response and strong $CD8^+$ T cell response, is expected to mitigate the risk of VAED/VAERD; [110,133] that immune profile is elicited by COVID-19 mRNA vaccine in clinical and preclinical studies.[134,135]

**Impact on the risk-benefit balance of the biologic product**

If there were an unfavourable balance in COVID-19 cases, including severe cases, in the pivotal clinical study between the vaccine and placebo groups, that may signal VAED/VAERD.

**Public health impact**

The potential risk of VAED/VAERD could have a public health impact if large populations of individuals are affected.

a. Search criteria for cases of potential VAED are: PTs Vaccine associated enhanced disease OR Vaccine associated enhanced respiratory disease OR Standard Decreased Therapeutic Response Search AND at least 1 of the following PTs Dyspnoea; Tachypnoea; Hypoxia; COVID 19 pneumonia; Respiratory Failure; Acute Respiratory Distress Syndrome; Cardiac Failure; Cardiogenic shock; Acute myocardial infarction; Arrhythmia; Myocarditis; Vomiting; Diarrhoea; Abdominal pain; Jaundice; Acute hepatic failure; Deep vein thrombosis; Pulmonary embolism; Peripheral Ischaemia; Vasculitis; Shock; Acute kidney injury; Renal failure; Altered state of consciousness; Seizure; Encephalopathy; Meningitis; Cerebrovascular accident; Thrombocytopenia; Disseminated intravascular coagulation; Chilblains; Erythema multiforme; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome in children;
Note: the "Standard Decreased Therapeutic Response" search include the Lack of efficacy PTs (Drug ineffective/Vaccination failure).
b. Please note that CT dataset from the safety database includes only cases reporting SAEs.
c. Includes cases where age in years was provided or where age was not provided, and age group was equal to child.

## SVII.3.2. Presentation of the Missing Information

### Table 64. 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 65. 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 66. 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 67. 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 68. Interaction with other Vaccines

Evidence source:
There are no data on interaction of COVID-19 mRNA vaccine with other vaccines at this time.

Population in need of further characterisation:
All reports describing interactions of COVID-19 vaccine with other vaccines per national recommendations in individuals will be collected and analysed as per routine PV activities. Interactions with commonly used non-COVID-19 vaccines, such as influenza vaccine, are proposed to be studied in a future clinical study (see PART III.2 and PART III.3).

### Table 69. Long Term Safety Data

Evidence source:
At this time, 6-month post dose 2 safety data are available for all patients who have received COVID-19 mRNA vaccine in Study C4591001. The study is ongoing.

Anticipated risk/consequence of missing information:
At the time of vaccine availability, the long-term safety of COVID-19 mRNA vaccine is not fully known, however there are no known risks with a potentially late onset. Data will continue to be collected from participants in ongoing study C4591001 for up to 2 years following the 2nd dose of vaccine. Additionally, active surveillance studies are planned to follow long-term safety in vaccine recipients for 2 years following Dose 2.

## Module SVIII. Summary of the Safety Concerns

### Table 70. Summary of Safety Concerns

| | |
|---|---|
| Important Identified Risks | Myocarditis and Pericarditis |
| Important Potential Risks | Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) |
| Missing Information | Use in pregnancy and while breast feeding |
| | Use in immunocompromised patients |
| | Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) |
| | Use in patients with autoimmune or inflammatory disorders |
| | Interaction with other vaccines |
| | Long term safety data |

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

## III.1. Routine Pharmacovigilance Activities

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

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

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

- Data Capture Aids have been created for this vaccine. They are intended to facilitate the capture of clinical details about:
    - the nature and severity of COVID-19 illness in individuals who have received the COVID-19 mRNA vaccine and is anticipated to provide insight into potential cases of vaccine lack of effect or VAED. The updated version of the DCA is provided in Annex 4.
    - potential multisystem inflammatory syndrome in children and adults (MIS-C/A) experienced by individuals following administration of Pfizer-BioNTech COVID-19 Vaccine. The DCA is provided in Annex 4.

Signal detection activities for the lifecycle of vaccines consist of individual AE assessment at case receipt, regular aggregate review of cases for trends and statistically disproportionately reported product-adverse event pairs. Aggregated and statistical reviews of data are conducted utilizing Pfizer's software interactive tools. Safety signal evaluation requires the collection, analysis and assessment of information to evaluate potential causal associations between an event and the product and includes subsequent qualitative or quantitative characterisation of the relevant safety risk to determine appropriate continued pharmacovigilance and risk mitigation actions. Signal detection activities for the COVID-19 mRNA vaccine occur on a weekly basis. In addition, observed versus expected analyses will be conducted as appropriate as part of routine signal management activity.

Routine signal detection activities for the COVID-19 mRNA vaccine will include routine and specific review of AEs consistent with the AESI list provided in PART II.SVII.1.1 - *Risks not considered important for inclusion in the list of safety concerns in the RMP.*

In addition, published literature is reviewed weekly for individual case reports and broader signal detection purposes.

Regulatory authority safety alerts monitoring.

The web-based AE reporting portal www.pfizersafetyreporting.com will be available for vaccine providers (e.g., pharmacists, nurses, physicians and others who administer vaccines) and recipients, to assist with anticipated high volume of reports (based on expectations of a large target population for vaccination). The portal will capture key adverse event data in the initial interaction and will provide automated intake into the Pfizer safety database via E2B for safety review.

At the country level, the Pfizer Drug Safety Units perform routine pharmacovigilance activities including the collection of AEs from various sources and the reporting of AEs to the regulatory authority as per local regulatory guidelines.

The serious adverse event (SAE)/product complaint (PC) Joint Report for Sterile Injectables is run monthly. In addition, the AE/PC Joint report and the AE/PC Lot/Lot profile Report is run quarterly and is a statistical report that identifies any data that could constitute a safety signal over time. The AE/PC Lot/Lot Profile report complements the monthly AE trending performed by Safety and the monthly PC trending performed by Product Quality.

**Summary safety reports**

The submission of summary safety reports complemented the submission of 6 monthly PSURs. 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.

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

- SmPC (section 6.6) contains instructions for reconstitution and administration, vaccination scheme, and storage conditions of the formulations of the COVID-19 mRNA vaccine.

- A poster with step-by-step instruction for vaccine storage, vial differentiation, dose planning and preparation, and administration is available, which can be conspicuously displayed in settings where vaccine is to be administered for ongoing reference.

- Brochures for safe handling of the vaccine and dry ice will accompany vaccine shipments.

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

- Medical information call centers will be available for healthcare providers to obtain information on use of the vaccine.

- Traceability and Vaccination Reminder card (Annex 7) will be provided with the pre-printed manufacturer name, placeholder spaces for dates of vaccinations and batch/lot numbers as a mitigation effort for potential confusion between vaccines. (See Traceability for additional details).

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

*Vial Differentiation*

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

## Table 71. Vaccine Presentation Characteristics

| Age group | 12 years and older | | | | 5 through 11 years | | 6 months through 4 years |
|---|---|---|---|---|---|---|---|
| **INN** | Tozinameran | Tozinameran | Tozinameran/ Riltozinameran | Tozinameran/ Famtozinameran | Tozinameran | Tozinameran/ Famtozinameran | Tozinameran |
| **Name** | Comirnaty 30 mcg/dose<br><br>DILUTE BEFORE USE<br><br>Purple Cap | Comirnaty 30 mcg/dose<br><br>DO NOT DILUTE<br><br>Grey Cap | Comirnaty Original/Omicron BA.1<br><br>DO NOT DILUTE<br><br>Grey Cap | Comirnaty Original/Omicron BA.4-5<br><br>DO NOT DILUTE<br><br>Grey Cap | Comirnaty 10 mcg/dose<br><br>DILUTE BEFORE USE<br><br>Orange cap | Comirnaty Original/Omicron BA.4-5<br><br>DILUTE BEFORE USE<br><br>Orange cap | Comirnaty 3 mcg/dose<br><br>DILUTE BEFORE USE<br><br>Maroon cap |
| **Dose** | 30 mcg (with dilution) | 30 mcg (no dilution) | 15/15 mcg (no dilution) | 15/15 mcg (no dilution) | 10 mcg (with dilution) | 5/5 mcg (with dilution) | 3 mcg (with dilution) |
| **Vial cap color and Label with Color Border** | Purple | Grey | Grey | Grey | Orange | Orange | Maroon |
| **Dose Volume** | 0.3 mL | 0.3 mL | 0.3 mL | 0.3 mL | 0.2 mL | 0.2 mL | 0.2 mL |
| **Amount of Diluent Needed per Vial** | 1.8 mL | NO DILUTION | NO DILUTION | NO DILUTION | 1.3 mL | 1.3 mL | 2.2 mL |
| **Fill Volume** | 0.45 mL | 2.25 mL | 2.25 mL | 2.25 mL | 1.3 mL | 1.3 mL | 0.4 mL |
| **Doses per vial** | 6 doses per vial (after dilution) | 6 doses per vial | 6 doses per vial | 6 doses per vial | 10 doses per vial (after dilution) | 10 doses per vial (after dilution) | 10 doses per vial (after dilution) |
| **Formulation** | PBS sucrose | Tris sucrose | Tris sucrose | Tris sucrose | Tris sucrose | Tris sucrose | Tris sucrose |

PBS = Phosphate Buffered Saline; Tris = Tromethamine Buffer or (HOCH2)3CNH

Large scale public health approaches for vaccination may represent changes to standard vaccine treatment process with the use of various formulations to different healthcare settings based on age (ie. less than 12 years and above 12 years of age). This represents the likelihood of the purple and grey vials co-existing in the same setting. These 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.

PBS-Sucrose formulation

**Comirnaty 30 mcg/ dose - 12 years of age and older, Dilute before use - Purple cap**: If 1.8 mL sodium chloride solution is not added to the 30 mcg/dose concentrate for dispersion for injection vial (purple cap), the user would only be able to extract approximately 1 dose instead of 6 doses as the filled volume is 0.45 mL.

Tris-Sucrose formulation

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

**Comirnaty 30 mcg/dose - 12 years of age and older, Do not dilute - Grey cap:** If attempted to further dilute the 30 mcg/dose dispersion for injection vial (gray cap), a user would immediately experience resistance to addition of any further volume, as the filled volume is 2.25 mL and therefore, there is little remaining physical space to add additional diluent to the vial.

**Comirnaty Original/Omicron BA.1 (15/15 mcg)/dose - 12 years of age and older, Do not dilute - Grey cap**: If attempted to further dilute the 30 mcg/dose dispersion for injection vial (grey cap), a user would immediately experience resistance to addition of any further volume, as the filled volume is 2.25 mL and therefore, there is little remaining physical space to add additional diluent to the vial.

**Comirnaty Original/Omicron BA.4-5 (15/15 mcg)/dose - 12 years of age and older, Do not dilute - Grey cap**: If attempted to further dilute the 30 mcg/dose dispersion for injection vial (grey cap), a user would immediately experience resistance to addition of any further volume, as the filled volume is 2.25 mL and therefore, there is little remaining physical space to add additional diluent to the vial.

**Comirnaty 10 mcg/dose - 5 through 11 years of age, Dilute before use - Orange cap**: If attempted to not dilute with 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 as the filled volume is 1.3 mL. If 1.8 mL of diluent, which is the dilution volume for the 30 mcg/dose diluted product (purple 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.

**Comirnaty Original/Omicron BA.4-5 (5/5 mcg)/dose - 5 through 11 years of age, Dilute before use - Orange cap**: If attempted to not dilute with 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 as the filled volume is 1.3 mL. If 2.2 mL of diluent, 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.

**Comirnaty 3 mcg/dose - 6 months through 4 years of age, Dilute before use - Maroon cap**: If attempted to not dilute 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 as the filled 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 under dilution would also reduce the number of doses retrieved out of the vial, which might indicate to the HCP that there had been an error in preparation.

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

**Traceability**

The SmPC, includes instructions for healthcare professionals:

- to clearly record the name and batch number of the administered vaccine to improve traceability (section 4.4).

- to report any suspected adverse reactions including batch/Lot number if available (section 4.8).

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

Additionally, alarms and escalation/notification for excursions (per pre-defined specifications) are programmed into the device. These data may be used for the assessment of a safety signal.

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

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

- Placeholder space for name of vaccinee;

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

In addition, to the Traceability and Vaccination Reminder cards, two stickers per dose, containing printed batch/lot information 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 in mass vaccination centers. We also acknowledge that some EU member states may require utilisation of nationally mandated vaccination cards or electronic systems to document batch/lot number; therefore, the available Traceability and Vaccination Reminder cards and stickers with printed lot/batch information may not be utilized in all member states.

The following milestones are proposed for the availability of the stickers with printed lot/batch information:

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

**Cold-Chain Handling and Storage**

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

- Each shipment of the vaccine is outfitted with a unique device that provides real-time monitoring of geographic location and temperature 24 hours per day, 7 days per week until delivery to a vaccinator's practice site. Alarms and escalation/notification to Pfizer on behalf of the MAH and/or to the recipient for excursions (per pre-defined specifications) are programmed into the device. Additionally, a shipment quality

report that indicates if the product is acceptable for immediate use is generated by Pfizer and transmitted to the vaccinator's practice site.

- Joint adverse event and product complaint (including available batch/lot information) trending reviews occur routinely with Global Product Quality.

- Additionally, available 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 20 studies, of which 5 global, 5 in Europe only, 7 in US only, 2 in US and Canada and 1 in New Zealand/Australia. There are 9 interventional studies (C4591001, C4591007, C4591015, BNT162-01 Cohort 13, C4591024, C4591031, C4591044, C4591048 and 1 study for vaccine interactions), 3 Low-Interventional studies (C4591036, WI235284 and WI255886) and 8 non-interventional studies (7 safety and 1 effectiveness), summarised in the table below and further detailed in Table 72 and Table 73.

| Study Number | Country | Interventional/ non-Interventional/ Low-Interventional | Purpose |
|---|---|---|---|
| C4591001 | Global | Interventional | Safety |
| C4591007 | Global | Interventional | Safety |
| C4591015 | Global | Interventional | Safety |
| C4591024[a] (former Safety and immunogenicity in high-risk adults) | Global | Interventional | Safety |
| C4591030 (Co-administration study with seasonal influenza vaccine) | NZ/AU | Interventional | Safety |
| C4591031 | Global | Interventional | Safety<br>Effectiveness |
| C4591044 | US | Interventional | Safety<br>Effectiveness |
| C4591048 | US | Interventional | Effectiveness[b] |
| BNT162-01 Cohort 13 | EU | Interventional | Safety |
| C4591009 | US | non-Interventional | Safety |
| C4591010 | EU | non-Interventional | Safety |
| C4591011 | US | non-Interventional | Safety |
| C4591012 | US | non-Interventional | Safety |
| C4591021 (former ACCESS/VAC4EU) | EU | non-Interventional | Safety |
| C4591022 | US/CA | non-Interventional | Safety |
| C4591038 (former C4591021 substudy) | EU | non-Interventional | Safety |
| C4591014 | US | non-Interventional | Effectiveness[b] |
| WI235284 | US | Low-Interventional[c] | Effectiveness[b] |
| WI255886 | EU[d] | Low-Interventional | Effectiveness[b] |
| C4591036 (former Pediatric Heart Network) | US/CA | Low-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.

*Non-Interventional Post Approval Safety Studies (8)*

The MAH proposes 8 complementary studies of real-world safety of COVID-19 mRNA vaccine that use multiple data sources and study designs. These are described in Table 72 below which includes the proposed post-approval safety studies that will be conducted in the EU and US.

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

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

- Additionally, C4591038 (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.

In addition to the studies in the EU, in support of the US BLA and sBLA applications, Pfizer will conduct 4 US studies and 1 US/CA for safety surveillance of COVID 19 mRNA. These studies include:

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

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

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

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

- 1 study will monitor rates of pregnancy and infant outcomes in planned and unplanned pregnancies exposed to BNT162b2 using an established pregnancy registry. Women receiving BNT162b2 during pregnancy will be followed from exposure to one-year post-partum. Analyses will be conducted to evaluate if the pregnant women receiving the vaccine during pregnancy experience increased risk of pregnancy and infant outcomes compared with 1) pregnant women who are unvaccinated and 2) pregnant women who have received an influenza or tetanus, diphtheria, and acellular pertussis (Tdap) vaccine during pregnancy (C4591022).

The protocols for the safety studies in the US (C4591009, C4591011, C4591012 and C4591022) were added in Annex 3 Part C.

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

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

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

To evaluate long-term outcomes, myocarditis/pericarditis-specific analytic endpoints in currently planned or ongoing studies C4591009, C4591011, C4591012, C4591021 and C4591038 (former C4591021 substudy) will assess the natural history of post-vaccination myo-/pericarditis, e.g., recovery status (medical record review) and/or identification of serious cardiovascular outcomes (structured data) within 1 year of myo-/pericarditis

diagnosis among individuals vaccinated with COMIRNATY as well as individuals not vaccinated with a COVID-19 vaccine.

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, studies C4591012, C4591021, and C4591036 will be assessed for the feasibility of studying the bivalent Omicron-modified vaccine. Feasibility is dependent on the ability to uniquely identify the bivalent vaccine as the booster dose administered. Additionally, the MAH has committed to the FDA to conduct a standalone post-authorization observational safety study to evaluate the Pfizer- BioNTech COVID-19 bivalent (Original and Omicron BA.4-5) vaccine and will provide a synopsis to the EMA and to the FDA in the near future .

*Non-Interventional Post-Approval Safety Studies that include paediatric subjects aged 5 to < 12 years old*

Studies C4591021(EU), C4591038 (former C4591021 substudy) (EU), C4591009 (US) C4591011 (US) and C4591036 (US and Canada) will assess the use of vaccine for the occurrence of safety events of interest, including myocarditis and pericarditis. Each of these studies includes individuals of all ages, including ages 5 to <12, except for 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 5 of the real-world safety studies (C4591009, C4591010, C4591011, C4591021 [former ACCESS/VAC4EU] and C4591022), described in Table 72. Study C4591012 is focused on patients in the Veterans Health Administration system and is not expected to capture many pregnancies given the demographics of the source population.

The findings from studies' interim analysis (where planned) will inform a strategy to assess pregnancy outcomes as vaccination in pregnancy expands. The MAH will consider established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In preGNancy) when developing any pregnancy related study objectives (currently not listed in Table 72 and Table 73).

The MAH agrees that monitoring vaccine safety in pregnant women is critical. Given that a pregnancy registry based on primary data collection is susceptible to non-participation, attrition, small sample size and limited or lack of comparator data, Pfizer, on behalf of the MAH, would like to propose monitoring vaccine safety in pregnancy using electronic health care data, which could be conducted in a representative pregnant woman population exposed

to the vaccine and minimize selection bias, follow-up bias, and reporting bias. In addition, internal comparison groups, such as contemporaneous unvaccinated pregnant women or women receiving other vaccine(s) to prevent COVID-19 (if available) could be included.

*Post-Approval Effectiveness Studies (3)*

Pfizer will conduct, on behalf of the MAA, at least one non-interventional study (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 illness in a real-world setting (C4591014). The effectiveness of COVID-19 mRNA vaccine will be estimated against laboratory confirmed COVID-19 illness requiring admission to the ED or hospital where SARS-CoV-2 is identified. This study will allow 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 and WI255886) added. The harmonisation of study definitions across these 3 protocols will allow for data and results comparison across study populations to provide a robust evidence base for evaluating the effectiveness of COVID-19 mRNA vaccine following its introduction into the real-world setting. The two studies, C4591014 and WI255886, will also assess the effectiveness of bivalent Omicron-modified vaccines following their introduction.

## Table 72. Additional Pharmacovigilance Activities

| **Study Number** *Country (ies)* | **Study Title** **Study Type** *Study Status* | **Rationale and Study Objectives** | **Study design** | **Study populations** | **Milestones** | |
|---|---|---|---|---|---|---|
| C4591001 Global | A Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-COV-2 RNA vaccine candidates against COVID-19 in healthy individuals.<br><br>Interventional *Ongoing* | The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine.<br><br>An imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2. | Phase 1/2/3, randomised, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals. | Healthy men and women 18-55 and 65-85 years of age.<br>Male and female, aged ≥ 12 years of age.<br>Stable chronic conditions including stable treated HIV, HBV and HCV allowed, excluding immunocompromising conditions and treatments. | CSR submission upon regulatory request: | Any time |
| | | | | | CSR submission 6 months post Dose 2: | 31-May-2021 |
| | | | | | Final CSR submission with supplemental follow-up: | 31-Dec-2023 |
| C4591007 Global | A phase 1, open-label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA | 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, | Healthy paediatric subjects and young adults. | Final CSR submission: | 03-Dec-2024[10] |

[10] The new timeline (endorsed by EMA on 24 March 2022) for availability of the final report is due to the amendments introduced over time to the study design.

## Table 72. Additional Pharmacovigilance Activities

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>*Study Status* | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| | vaccine candidate against COVID-19 in healthy children and young adults.<br>Interventional<br>*Ongoing* | | tolerability, immunogenicity, and efficacy | | | |
| C4591009<br>US | A non-interventional post approval safety study Pfizer-BioNTech COVID-19 vaccine in the United States.<br><br>non-Interventional<br>*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 electronic health records and claims data from data partners participating in the Sentinel System. | Post-approval observational study using real-world data. | The general US population (all ages), pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System.<br>This study will include an analysis of individuals who receive a booster dose of the Pfizer-BioNTech COVID-19 vaccine. | Protocol submission: | 31-Aug-2021 |
| | | | | | Protocol amendment submission: | 11-Jul-2022 |
| | | | | | Monitoring report 1 submission: | 31-Oct-2022 |
| | | | | | Monitoring report 2 submission: | 31-Oct-2024 |
| | | | | | Interim Analysis submission: | 31-Oct-2023 |

## Table 72. Additional Pharmacovigilance Activities

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>*Study Status* | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| | | | | | Final CSR submission: | 31-Mar-2026[11] |
| C4591011<br>US | Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense population following Emergency Use Authorization.<br><br>non-Interventional<br>*Planned* | To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, including myocarditis and pericarditis following receipt of the COVID-19 mRNA vaccine. | Secondary use of real-world data to conduct comparative analyses using self-controlled risk interval and active comparator approaches. The study will conduct active surveillance of individuals who receive a booster dose of the Pfizer-BioNTech COVID-19 vaccine. | Department of Defense military and civilian personnel and their families (all ages) in the Military Health System. | Interim reports submission: | 30-Sep-2022 |
| | | | | | | 31-Dec-2022 |
| | | | | | Final CSR submission: | 31-Dec-2023 |
| C4591012<br>US | Post-Emergency Use Authorization active safety surveillance study among individuals in the Veteran's Affairs health system receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. | To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, including myocarditis and pericarditis, following | Secondary use of real-world data to conduct comparative analyses using self-controlled risk interval and active comparator approaches. | US Veterans | Interim reports submission: | 30-Jun-2021 |
| | | | | | | 31-Dec-2021 |
| | | | | | | 30-Jun-2022 |
| | | | | | | 31-Dec-2022 |

[11] 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

## Table 72. Additional Pharmacovigilance Activities

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>*Study Status* | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| | non-Interventional<br>*Ongoing* | receipt of the COVID-19 mRNA vaccine including the bivalent Omicron-modified vaccine, if feasible. | The study will also conduct active surveillance of individuals who receive a booster dose of the Pfizer-BioNTech COVID-19 vaccine including the bivalent Omicron-modified vaccine if feasible. | | Protocol amendment submission (booster dose): | 30-Nov-2021 |
| | | | | | Final CSR submission: | 31-Dec-2023 |
| C4591010<br>EU | A Non-Interventional Post-Authorization Safety Study (PASS) for Active Safety Surveillance of recipients of the Pfizer-BioNTech COVID-19 mRNA vaccine in the EU.<br><br>non-Interventional<br>*Ongoing* | To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates. | Primary data collection cohort study<br><br>This study will also conduct active surveillance of individuals who receive a booster dose of the Pfizer-BioNTech COVID-19 vaccine. | EU general population. | Final CSR submission: | 30-Sep-2024 |

## Table 72. Additional Pharmacovigilance Activities

| **Study Number** *Country (ies)* | **Study Title** **Study Type** *Study Status* | **Rationale and Study Objectives** | **Study design** | **Study populations** | **Milestones** | |
|---|---|---|---|---|---|---|
| C4591015<br>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.<br><br>Interventional<br>*Ongoing* | To assess safety and immunogenicity in pregnant women<br><br>In addition, exploratory objectives include:<br><br>(a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.<br><br>(b) To describe the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. | Randomised, placebo-controlled, observer-blind study. | Healthy pregnant women 18 years of age or older vaccinated during their 24 to 34 weeks of gestation. | Final CSR submission: | 30-Apr-2023 |
| C4591014<br>US | Pfizer-BioNTech COVID-19 BNT162b2 vaccine effectiveness study - Kaiser | To determine the effectiveness of COVID-19 mRNA vaccine and of the bivalent Omicron-modified | Non-interventional study (test-negative design) of individuals | Individuals ≥ 6 months of age with acute respiratory illness admitted to the | Final CSR submission: | 30-Jun-2023 |

## Table 72. Additional Pharmacovigilance Activities

| **Study Number** *Country (ies)* | **Study Title** **Study Type** ***Study Status*** | **Rationale and Study Objectives** | **Study design** | **Study populations** | **Milestones** | |
|---|---|---|---|---|---|---|
| | Permanente Southern California Non-Interventional (Retrospective database analysis).<br><br>non-Interventional<br>*Ongoing* | vaccine when administered outside of the clinical setting.<br><br>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. | presenting with symptoms of potential COVID-19 illness in a real-world setting. | emergency department or hospital. | Protocol amendment (for bivalent Omicron-modified vaccine) submission: | 31-Dec-2022 |
| | | | | | Final CSR (for bivalent Omicron-modified vaccine) submission: | 30-Jun-2024 |

## Table 72. Additional Pharmacovigilance Activities

| **Study Number**<br>***Country (ies)*** | **Study Title**<br><br>**Study Type**<br>***Study Status*** | **Rationale and Study Objectives** | **Study design** | **Study populations** | **Milestones** | |
|---|---|---|---|---|---|---|
| WI235284<br>US | Determining RSV burden and outcomes in pregnant women and older adults requiring hospitalization. COVID-19 Amendment for COVID VE / Sub-study 6.<br><br>Low-Interventional[a]<br>*Ongoing* | To determine the effectiveness of COVID-19 mRNA vaccine when administered outside of the clinical setting.<br><br>To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection. | Low-interventional study (test-negative design) of individuals presenting with symptoms of potential COVID-19 illness in a real-world setting. | Individuals ≥18 years of age with acute respiratory illness admitted to the hospital. | Final CSR submission: | 30-Jun-2023 |
| WI255886<br>Ex-EU[b] | Avon Community Acquired Pneumonia Surveillance Study. A pan-pandemic acute lower respiratory tract disease surveillance study.<br><br>Low-Interventional[a]<br>*Ongoing* | To determine the effectiveness of COVID-19 mRNA vaccine and of the bivalent Omicron-modified vaccine when administered outside of the clinical setting.<br><br>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 | 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 |
| | | | | | Protocol amendment (for bivalent Omicron-modified vaccine) submission: | 31-Dec-2022 |
| | | | | | Final CSR (for bivalent Omicron-modified | 30-Jun-2024 |

## Table 72. Additional Pharmacovigilance Activities

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>*Study Status* | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| | | of bivalent Omicron-modified vaccines following their introduction in individuals 18 years of age and older. | | | vaccine) submission: | |
| BNT162-01<br>Cohort 13<br>EU | Immunogenicity of Pfizer-BioNTech COVID-19 vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses.<br><br>Interventional<br>*Ongoing* | To assess potentially protective immune responses in immunocompromised adults. | Dose escalating<br>Open uncontrolled. | Use in immunocompromised patients. | IA submission: | 30-Sep-2021 |
| | | | | | Final CSR submission: | 31-Oct-2023[12] |
| C4591024 (former Safety and immunogenicity in high-risk adults) | A Phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine | Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: | Open uncontrolled. | High risk individuals including frail, those having autoimmune disease, chronic renal | Protocol submission: | 30-Jun-2021 |

[12] Protocol amendment 6.0 implemented three additional cohorts which led to increase of study duration and postponing of final study report submission (endorsed by EMA on 16 May 2022)

## Table 72. Additional Pharmacovigilance Activities

| **Study Number** *Country (ies)* | **Study Title** **Study Type** ***Study Status*** | **Rationale and Study Objectives** | **Study design** | **Study populations** | **Milestones** | |
|---|---|---|---|---|---|---|
| Global | candidate BNT162b2 in immunocompromised participants ≥2 years of age.<br><br>Interventional<br>*Ongoing* | NSCLC, CLL, in hemodialysis for end-stage renal disease). | | disease and immunocompromising conditions. | Final CSR submission: | 30-Jun-2023[13] |
| 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.<br><br>non-Interventional<br>*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 the bivalent Omicron modified vaccine in all authorized age groups, | Secondary database analysis of observational data to assess potential increased risk of adverse events of special interest (AESI and other clinically significant events among | EU General population (all ages). | Protocol amendment submission (booster dose): | 30-Sep-2024 |

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

## Table 72. Additional Pharmacovigilance Activities

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>*Study Status* | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| | | including individuals less than 12 years of age, if feasible.<br><br>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. | 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. | | Final CSR submission: | 30-Sep-2024[14] |
| 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.<br><br>non-Interventional | Assessment of the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as | 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 |

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

## Table 72. Additional Pharmacovigilance Activities

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>*Study Status* | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| | *Planned* | individuals not vaccinated with a COVID-19 vaccine. | | | | |
| C4591022<br>US/Canada | Pfizer-BioNTech COVID-19 Vaccine exposure during pregnancy: A non-interventional post-approval safety study of pregnancy and infant outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry.<br><br>non-Interventional<br>*Ongoing* | To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age. | Analyses will be conducted to evaluate if the pregnant women receiving the vaccine during pregnancy experience increased risk of pregnancy and infant outcomes compared with 1) pregnant women who are unvaccinated and 2) pregnant women who have received an influenza or tetanus, diphtheria, and acellular pertussis (Tdap) vaccine during pregnancy | Pregnant women and infant outcomes | Interim reports submission: | 31-Jan-2022 |
| | | | | | | 31-Jan-2023 |
| | | | | | | 31-Jan-2024 |
| | | | | | Final CSR submission: | 31-Dec-2024 |

## Table 72. Additional Pharmacovigilance Activities

| **Study Number** *Country (ies)* | **Study Title** **Study Type** *Study Status* | **Rationale and Study Objectives** | **Study design** | **Study populations** | **Milestones** | |
|---|---|---|---|---|---|---|
| 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<br><br>Low-Interventional *Planned* | To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis including myocarditis after the bivalent Omicron-modified vaccine, if feasible. | 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 |
| | | | | | Final CSR submission: | 31-Dec-2029[15] |
| C4591030 (Co-administration study with seasonal influenza vaccine) NZ, AU | Co-administration of BNT162b2 with seasonal influenza vaccine. Interventional *Completed* | Safety and immunogenicity of COVID-19 mRNA vaccine and quadrivalent seasonal influenza vaccine when administered separately or concomitantly. | This is a randomised comparison of safety and immunogenicity of COVID-19 mRNA vaccine and a quadrivalent influenza vaccine administered | General population | Protocol submission: | 17-Aug-2021[16] |
| | | | | | Final CSR submission: | 28-Feb-2023[17] |

[15] 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

[16] Actual Submission date

[17] Due to limited lab capacity and competing priorities on the COVID-19 programme, the serology data for Study C4591030 will now not be available until April 2023. The final CSR is therefore now expected to be available for submission to the agency by 31 August 2023. The final CSR for this study is an RMP commitment with current due date 28 February 2023. The deadline was previously extended from 31 December 2022 via PAM 18.3(EMEA/H/C/0057/MEA/018)

## Table 72. Additional Pharmacovigilance Activities

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>*Study Status* | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| | | | concomitantly and one month apart. | | | |
| C4591031<br>Substudy E<br>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 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.<br><br>Interventional<br>*Ongoing* | 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.<br><br>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. | The sentinel-cohort participants randomized to the combination BNT162b2 and BNT162b2 OMI groups will be administered a suspension containing a mixture of 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 | Participants:<br>> 55 years of age<br>18- to 55 years of age | Interim reports submission (> 55 y): | 31-Aug-2022 |
| | | | | | Interim reports submission (18 – to 55 y): | 31-Oct - 2022 |
| | | | | | 6M Final CSR submission (>55 y): | 31-Jan - 2023 |
| | | | | | 6M Final CSR submission (18- to 55 y): | 30-Mar 2023 |

## Table 72. Additional Pharmacovigilance Activities

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>*Study Status* | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| C4591044<br>US | An Interventional, Randomized, Active-Controlled, Phase 2 Observer-Blind 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<br><br>Interventional<br>*Ongoing* | Study boosting strategies against variants of concern<br><br>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 | <u>Cohort 1:</u><br>randomized, active-controlled, observer-blind study<br><br>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:<br><br>• BNT162b5 Bivalent (WT/OMI BA.2)<br>• BNT162b2 Bivalent (WT/OMI BA.1)<br><br><u>Cohort 2 (PA1):</u><br>Participants 12 through 17 years of age will receive a single dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg as a second booster dose (open label). Participants 18-55 and >55 years of age | Healthy male and female participants ≥12 years of age.<br><br>Stable chronic conditions including stable treated HIV, HBV and HCV allowed. | Protocol submission: | 14-Jun-2022 |
| | | | | | Protocol amendment 1 submission: | 28-Jul-2022 |
| | | | | | Protocol amendment 2 submission: | 23-Sep-2022 |
| | | | | | Final CSR submission: | 30-Sep-2023 |

## Table 72. Additional Pharmacovigilance Activities

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>*Study Status* | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| | | | will be randomized 1:1 within each age group to receive either BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at 30 µg or 60 µg as a second booster dose (observer-blind). | | | |
| C4591048<br>US | 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.<br><br>Interventional<br>*Ongoing* | To study 3rd and/or 4th doses or primary series against variants of concern.<br><br>To describe the safety/tolerability and immune response to bivalent BNT162b2. | SSB, SSC, SSD: 3rd and/or 4th dose to COVID-19-vaccine-experienced participants 6 months to < 12 years of age.<br><br>SSA: primary bivalent series in COVID-19 vaccine-naïve participants 6 months to <2 years. | 6 months to < 12 years (SSB, SSC, SSD).<br><br>6 months to <2 years (SSA). | Protocol submission | 23-Sep-2022 |
| | | | | | Final CSR submission | 31-May-2025 |

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 73. On-going and Planned Additional Pharmacovigilance Activities

| Study (*study short name, and title*)<br>Status (*planned/on-going*) | Country | Summary of Objectives | Safety concerns addressed | Milestone | Due dates |
|---|---|---|---|---|---|
| **Category 3** | | | | | |
| C4591001<br>*Ongoing* | Global | The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine.<br>An imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease.<br>Surveillance is planned for 2 years following Dose 2. | Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)<br>Use in frail patients with co-morbidities (C4591001 subset)<br>Long term safety data. | CSR submission upon regulatory request: | Any time |
| | | | | CSR submission 6 months post Dose 2: | 31-May-2021 |
| | | | | Final CSR submission with supplemental follow-up: | 31-Dec-2023 |
| C4591007<br>*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. | Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)<br>Long term safety data. | Final CSR submission: | 03-Dec-2024[10] |
| C4591009<br>*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<br>Use in pregnancy<br>Use in immunocompromised patients | Protocol submission: | 31-Aug-2021 |
| | | | | Protocol amendment submission: | 11-Jul- 2022 |
| | | | | Monitoring report 1 submission: | 31-Oct-2022 |
| | | | | Monitoring report 2 submission: | 31-Oct-2024 |

## Table 73. On-going and Planned Additional Pharmacovigilance Activities

| Study (*study short name, and title*)<br>Status (*planned/on-going*) | Country | Summary of Objectives | Safety concerns addressed | Milestone | Due dates |
|---|---|---|---|---|---|
| | | | | Interim Analysis submission: | 31-Oct-2023 |
| | | | | Final CSR submission: | 31-Mar-2026[11] |
| C4591011<br>*Planned* | US | To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine. | Myocarditis and pericarditis<br>AESI-based safety events of interest including vaccine associated enhanced disease<br>Use in pregnancy<br>Use in immunocompromised patients<br>Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)<br>Use in patients with autoimmune or inflammatory disorders<br>Long-term safety data. | Interim reports submission: | 30-Sep-2022 |
| | | | | | 31-Dec-2022 |
| | | | | Final CSR submission: | 31-Dec-2023 |
| C4591012<br>*Ongoing* | US | | Myocarditis and pericarditis<br>AESI-based safety events of interest including vaccine associated enhanced disease | Interim reports submission: | 30-Jun-2021 |
| | | | | | 31-Dec-2021 |
| | | | | | 30-Jun-2022 |
| | | | | | 31-Dec-2022 |

## Table 73. On-going and Planned Additional Pharmacovigilance Activities

| **Study (*study short name, and title*)**<br>**Status (*planned/on-going*)** | **Country** | **Summary of Objectives** | **Safety concerns addressed** | **Milestone** | **Due dates** |
|---|---|---|---|---|---|
| | | To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine including the bivalent Omicron modified vaccine, if feasible. | Use in immunocompromised patients.<br>Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)<br>Use in patients with autoimmune or inflammatory disorders<br>Long-term safety data. | Final CSR submission | 31-Dec-2023 |
| C4591010<br>*Ongoing* | EU | To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates. | AESI-based safety events of interest<br>Use in pregnancy<br>Long-term safety data. | Final CSR submission | 30-Sep-2024 |

## Table 73. On-going and Planned Additional Pharmacovigilance Activities

| **Study (*study short name, and title*)**<br>**Status (*planned/on-going*)** | **Country** | **Summary of Objectives** | **Safety concerns addressed** | **Milestone** | **Due dates** |
|---|---|---|---|---|---|
| C4591015<br>*Ongoing* | Global | To assess safety and immunogenicity in pregnant women<br><br>In addition, exploratory objectives include:<br>(a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.<br><br>(b) To describe the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. | Use in pregnancy and while breast feeding. | Final CSR submission: | 30-Apr-2023 |
| C4591014<br>*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. | Final CSR submission: | 30-Jun-2023 |
| | | | | Protocol amendment (for bivalent Omicron-modified vaccine) submission: | 31-Dec- 2022 |
| | | | | Final CSR (for bivalent Omicron-modified vaccine) submission: | 30-Jun- 2024 |

## Table 73. On-going and Planned Additional Pharmacovigilance Activities

| Study (*study short name, and title*)<br>Status (*planned/on-going*) | Country | Summary of Objectives | Safety concerns addressed | Milestone | Due dates |
|---|---|---|---|---|---|
| WI235284<br>*Ongoing* | US[a] | To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection. | Not Applicable. | Final CSR submission: | 30-Jun-2023 |
| WI255886<br>*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. | Final CSR submission: | 30-Jun-2023 |
| | | | | Protocol amendment (for bivalent Omicron-modified vaccine) submission: | 31-Dec- 2022 |
| | | | | Final CSR (for bivalent Omicron-modified vaccine) submission: | 30-Jun- 2024 |
| BNT162-01<br>Cohort 13<br>*Ongoing* | EU | To assess potentially protective immune responses in immunocompromised adults. | Use in immunocompromised patients. | IA submission: | 30-Sep-2021 |
| | | | | Final CSR submission: | 31-Oct-2023[12] |

## Table 73. On-going and Planned Additional Pharmacovigilance Activities

| Study (*study short name, and title*)<br>Status (*planned/on-going*) | Country | Summary of Objectives | Safety concerns addressed | Milestone | Due dates |
|---|---|---|---|---|---|
| C4591024 (former Safety and immunogenicity in high-risk adults)<br>*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<br>Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)<br>Use in patients with autoimmune or inflammatory disorders. | Protocol submission: | 30-Jun-2021 |
| | | | | Final CSR submission: | 30-Jun-2023[13] |
| C4591021 (former ACCESS/VAC4EU)<br>*Ongoing* | EU | Assessment of potential increased risk of adverse events of special interest (AESI) after being vaccinated with COVID-19 mRNA vaccine including bivalent Omicron modified vaccine in all authorized age groups, including individuals less than 12 years of age, if feasible.<br><br>Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination. | Myocarditis and Pericarditis<br>AESI-based safety events of interest including vaccine associated enhanced disease<br>Use in pregnancy<br>Use in immunocompromised patients<br>Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)<br>Use in patients with autoimmune or inflammatory disorders<br>Long term safety data. | Final CSR submission: | 30-Sep-2024 |
| C4591038 (former C4591021 substudy)<br>*Planned* | EU | | Myocarditis and Pericarditis<br>Long term safety data. | Protocol submission: | 31-Jan-2022 |

## Table 73. On-going and Planned Additional Pharmacovigilance Activities

| Study (*study short name, and title*)<br>Status (*planned/on-going*) | Country | Summary of Objectives | Safety concerns addressed | Milestone | Due dates |
|---|---|---|---|---|---|
| | | To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine. | | Final CSR submission: | 30-Sep-2024 |
| C4591022<br>*Ongoing* | US/CA | To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age. | Use in pregnancy. | Interim reports submission: | 31-Jan-2022 |
| | | | | | 31-Jan-2023 |
| | | | | | 31-Jan-2024 |
| | | | | Final CSR submission: | 31-Dec-2024 |
| C4591036 (former Pediatric Heart Network Study)<br>*Planned* | US/CA | To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis including myocarditis after the bivalent Omicron modified vaccine, if feasible. | Myocarditis/pericarditis<br>Long term safety data. | Protocol submission: | 30-Nov-2021 |
| | | | | Final CSR submission: | 31-Dec-2029[15] |

## Table 73. On-going and Planned Additional Pharmacovigilance Activities

| Study (*study short name, and title*)<br>Status (*planned/on-going*) | Country | Summary of Objectives | Safety concerns addressed | Milestone | Due dates |
|---|---|---|---|---|---|
| C4591030 (Co-administration study with seasonal influenza vaccine)<br>*Completed* | Australia, New Zealand | Safety and immunogenicity of COVID-19 mRNA vaccine and quadrivalent seasonal influenza vaccine when administered separately or concomitantly. | Interaction with other vaccines. | Protocol submission: | 17 Aug 2021 |
| | | | | Final CSR submission: | 28-Feb-2023[17] |
| C4591031 Substudy E<br>*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.<br><br>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. | Not applicable[c]<br>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 (>55 y): | 31-Jan-2023 |
| | | | | 6M Final CSR submission (18- to 55 y): | 30-Mar 2023 |
| C4591044<br>*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]<br>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: | 30-Sep-2023 |

## Table 73. On-going and Planned Additional Pharmacovigilance Activities

| Study (*study short name, and title*)<br>Status (*planned/on-going*) | Country | Summary of Objectives | Safety concerns addressed | Milestone | Due dates |
|---|---|---|---|---|---|
| C4591048<br>*Ongoing* | US | To describe the safety/tolerability and immune response to bivalent BNT162b2 given as:<br><br>SSB, SSC, SSD: 3rd and/or 4th dose to COVID-19-vaccine-experienced participants 6 months to < 12 years of age<br><br>SSA: primary bivalent series in COVID-19 vaccine-naïve participants 6 months to <2 years. | Not applicable[c] | Protocol Submission: | 23-Sep-2022 |
| | | | | Final CSR submission: | 31-May-2025 |

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 74. Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety Concern | Routine risk minimisation activities |
|---|---|
| **Important Identified Risk** | |
| Myocarditis and Pericarditis | Routine risk communication:<br>SmPC section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk: None.<br><br>Other routine risk minimisation measures beyond the Product Information: None. |
| **Important Potential Risk** | |
| Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) | Routine risk communication: None.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk: None.<br><br>Other routine risk minimisation measures beyond the Product Information: None. |
| **Missing Information** | |
| Use in pregnancy and while breast feeding | Routine risk communication:<br>SmPC section 4.6 Fertility, pregnancy and lactation<br>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).<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk: None.<br><br>Other routine risk minimisation measures beyond the Product Information: None. |
| Use in immunocompromised patients | Routine risk communication:<br>SmPC section 4.4 Special warnings and precautions for use and section 5.1 Pharmacodynamic properties. |

**Table 74. Description of Routine Risk Minimisation Measures by Safety Concern**

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

## V.2. Additional Risk Minimisation Measures

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

## Table 75. 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.<br><br>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 76. 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:<br><br>SmPC sections 4.4. and 4.8.<br><br>Additional risk minimisation measures:<br><br>DHCP letter and communication plan (see V.2 and Annex 6). | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>Studies (Final CSR Due Date)<br>C4591009 (31-Mar-2026)<br>C4591011 (31-Dec-2023)<br>C4591012 (31-Dec-2023)<br>C4591021 (former ACCESS/VAC4EU) (30-Sep-2024).<br>C4591038 (former C4591021 substudy) (30-Sep-2024)<br>C4591036 [former Pediatric Heart Network study] (31-Dec-2029). |
| Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) | Routine risk minimisation measures:<br><br>None.<br><br>Additional risk minimisation measures:<br><br>No risk minimisation measures. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>DCA is intended to facilitate the capture of clinical details about the nature and severity of COVID-19 illness in individuals who have received the COVID-19 mRNA vaccine and is anticipated to provide insight into potential cases of vaccine lack of effect or VAED (PART III.1 and Annex 4).<br><br>Additional pharmacovigilance activities:<br><br>Studies (Final CSR Due Date)<br>C4591001 (31-Dec-2023)<br>C4591007 (03-Dec-2024)<br>C4591009 (31-Mar-2026)<br>C4591011[b] (31-Dec-2023)<br>C4591012[b] (31-Dec-2023)<br>C4591021 (former ACCESS/VAC4EU) (30 Sep-2024)[b]. |
| Use in pregnancy and while breast feeding | Routine risk minimisation measures:<br>SmPC section 4.6; PL section 2.<br><br>Additional risk minimisation measures: | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>Studies (Final CSR Due Date)<br>C4591009 (31-Mar-2026) |

## Table 76. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| | No risk minimisation measures. | C4591010[a](30-Sep-2024)<br>C4591011[a] (31-Dec-2023)<br>C4591015 (30-Apr-2023)<br>C4591021 (former ACCESS/VAC4EU)[a] (30-Sep-2024).<br>C4591022[a] (31-Dec-2024) |
| Use in immunocompromised patients | Routine risk minimisation measures:<br><br>SmPC sections 4.4 and 5.1.<br><br>Additional risk minimisation measures:<br><br>No risk minimisation measures. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>Studies (Final CSR or IA Due Date)<br>BNT162-01 Cohort 13 (IA: 30-Sep-2021, CSR: 31-Oct-2023)<br>C4591010[c] (30-Sep-2024)<br>C4591011 (31-Dec-2023)<br>C4591012 (31-Dec-2023)<br>C4591021 (former ACCESS/VAC4EU) (30-Sep-2024)<br>C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)[13] |
| Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) | Routine risk minimisation measures:<br><br>SmPC section 5.1.<br><br>Additional risk minimisation measures:<br><br>No risk minimisation measures. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>Studies (Final CSR Due Date)<br>C4591001 subset (31-Dec-2023)<br>C4591011 (31-Dec-2023)<br>C4591012 (31-Dec-2023)<br>C4591021 (former ACCESS/VAC4EU) (30-Sep-2024)<br>C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)[13] |
| Use in patients with autoimmune or inflammatory disorders | Routine risk minimisation measures:<br><br>None.<br>Additional risk minimisation measures: | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br>Studies (Final CSR Due Date)<br>C4591011 (31-Dec-2023)<br>C4591012 (31-Dec-2023) |

## Table 76. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| | No risk minimisation measures. | C4591021 (former ACCESS/VAC4EU) (30-Sep-2024)<br>C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)[13] |
| Interaction with other vaccines | Routine risk minimisation measures:<br><br>SmPC section 4.5.<br><br>Additional risk minimisation measures:<br><br>No risk minimisation measures. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>Studies (Final CSR Due Date)<br>C4591030 (Co-administration study with seasonal influenza vaccine) (28-Feb-2023). |
| Long term safety data | Routine risk minimisation measures:<br><br>None.<br><br>Additional risk minimisation measures:<br><br>No risk minimisation measures. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>Studies (Final CSR Due Date)<br>C4591001 (31-Dec-2023)<br>C4591007 (03-Dec-2024)<br>C4591010 (30-Sep-2024)<br>C4591011 (31-Dec-2023)<br>C4591012 (31-Dec-2023)<br>C4591021 (former ACCESS/VAC4EU) (30-Sep-2024).<br>C4591038 (former C4591021 substudy) (30-Sep-2024)<br>C4591036 (former PHN) (31-Dec-2029) |

a. Please note that studies C4591009, C4591010, C4591011, C4591021 (former ACCESS/VAC4EU) and C4591022 address only “Use in pregnancy” and not “Breast feeding”.
b. Addresses AESI-based safety events of interest including vaccine associated enhanced disease
c. Addresses AESI-based safety events of interest.

# PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

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

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

Comirnaty, Comirnaty Original/Omicron BA.1 (15/15 micrograms) and Comirnaty Original/Omicron BA.4-5 (15/15 and 5/5 micrograms) 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 (15/15 and 5/5 micrograms) should be used.

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

## I. The Medicine and What It Is Used For

Comirnaty is a vaccine for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 6 months of age and older. Comirnaty Original/Omicron BA.1 (15/15 micrograms) and Comirnaty Original/Omicron BA.4-5 (15/15 and 5/5 micrograms) /dose dispersion for injection are indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older (BA.1) and 5 years of age and older (BA.4-5) who have previously received at least a primary vaccination course against COVID-19 (see SmPC for the full indication). Both 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) and of Comirnaty Original/Omicron BA.4-5 (15/15 and 5/5 micrograms) benefits can be found in Comirnaty’s, Comirnaty Original/Omicron BA.1 (15/15 micrograms) and Comirnaty Original/Omicron BA.4-5 (15/15 and 5/5 micrograms)

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) and of Comirnaty Original/Omicron BA.4-5 (15/15 and 5/5 micrograms), 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) and Comirnaty Original/Omicron BA.4-5 (15/15 and 5/5 micrograms) 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 (15/15 and 5/5 micrograms) 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) and of Comirnaty Original/Omicron BA.4-5 (15/15 and 5/5 micrograms) 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) and Comirnaty Original/Omicron BA.4-5 (15/15 and 5/5 micrograms). 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 77. List of Important Risks and Missing Information**

| | |
|---|---|
| Important identified risks | Myocarditis and Pericarditis |
| Important potential risks | Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) |
| Missing information | Use in pregnancy and while breast feeding |
| | Use in immunocompromised patients |
| | Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) |
| | Use in patients with autoimmune or inflammatory disorders |
| | Interaction with other vaccines |
| | Long term safety data |

## II.B Summary of Important Risks

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

**Table 78. 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:<br>SmPC sections 4.4. and 4.8.<br><br>Additional risk minimisation measures:<br>DHCP letter and communication plan |
| Additional pharmacovigilance activities | C4591009<br>C4591011<br>C4591012<br>C4591021 (former ACCESS/VAC4EU)<br>C4591038 (former C4591021 sub-study)<br>C4591036 (former Pediatric Heart Network study)<br>See Section II.C this summary for an overview of the post-authorisation development plan. |

## Table 79. Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

| | |
|---|---|
| Evidence for linking the risk to the medicine | VAED is considered a potential risk because it has not been seen in human studies with this or other COVID-19 vaccines being studied. It has not been seen in vaccine studies in animal models of the SARS-CoV-2 virus either. However, in selected vaccine studies in animal models as well as in some laboratory studies in animal cells infected with 2 other related coronaviruses (SARS-CoV-1 and MERS-CoV), abnormalities in immune responses or cellular responses indicative of VAED were observed. Because of this, VAED is considered a potential risk. In the past there have been other examples of particularly respiratory viruses where VAED has been observed. For example, some children who received an inactivated respiratory syncytial virus vaccine (a different type of virus), had worse signs of disease when they were subsequently infected with respiratory syncytial virus.<br>VAED is thought to occur by several mechanisms where the immune response is not fully protective and actually either causes the body to have an inflammatory reaction due to the type of immune response with specific types of T-cells, or the body does not produce enough strong antibodies to prevent SARS-CoV-2 infection of cells or produces weak antibodies that actually bind to the virus and help it to enter cells more easily, leading to worse signs of disease. |
| Risk factors and risk groups | It is thought that the potential risk of VAED may be increased in individuals producing a weak antibody response or in individuals with decreasing immunity over time. |
| Risk minimisation measures | Routine risk minimisation measures:<br>None.<br><br>Additional risk minimisation measures:<br>None. |
| Additional pharmacovigilance activities | C4591001<br>C4591007<br>C4591009[a]<br>C4591011[a]<br>C4591012[a]<br>C4591021 (former ACCESS/VAC4EU)[a]See Section II.C of this summary for an overview of the post-authorisation development plan. |

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

## Table 80. Missing Information: Use in Pregnancy and while Breast Feeding

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC section 4.6; PL section 2.<br><br>Additional risk minimisation measures:<br>No risk minimisation measures. |
| Additional pharmacovigilance activities | C4591009[a]<br>C4591010[a]<br>C4591011[a]<br>C4591015<br>C4591021 (former ACCESS/VAC4EU)[a]<br>C4591022[a]<br><br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

a. Please note that studies C4591009, C4591010, C4591011, C4591021 (former ACCESS/VAC4EU) and C4591022 address only "Use in pregnancy" and not "Breast feeding".

## Table 81. Missing Information: Use in Immunocompromised Patients

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.4 and 5.1.<br><br>Additional risk minimisation measures:<br>No risk minimisation measures. |
| Additional pharmacovigilance activities | BNT162-01 cohort 13<br>C4591010[a]<br>C4591011<br>C4591012<br>C4591021 (former ACCESS/VAC4EU)<br>C4591024 (former Safety and Immunogenicity in high-risk adults)<br><br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

a. Addresses AESI-based safety events of interest

### Table 82. 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:<br>SmPC section 5.1.<br><br>Additional risk minimisation measures:<br>No risk minimisation measures. |
| Additional pharmacovigilance activities | C4591001 subset<br>C4591011<br>C4591012<br>C4591021 (former ACCESS/VAC4EU)<br>C4591024 (former Safety and immunogenicity in high-risk adults)<br><br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

### Table 83. Missing Information: Use in Patients with Autoimmune or Inflammatory Disorders

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>None.<br><br>Additional risk minimisation measures:<br>No risk minimisation measures. |
| Additional pharmacovigilance activities | C4591011<br>C4591012<br>C4591021 (former ACCESS/VAC4EU)<br>C4591024 (former Safety and immunogenicity in high-risk adults)<br><br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

### Table 84. Missing Information: Interaction with other Vaccines

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC section 4.5.<br><br>Additional risk minimisation measures:<br>No risk minimisation measures. |
| Additional pharmacovigilance activities | C4591030 (Co-administration study with seasonal influenza vaccine)<br><br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 85. Missing Information: Long Term Safety Data**

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>None.<br><br>Additional risk minimisation measures:<br>No risk minimisation measures. |
| Additional pharmacovigilance activities | C4591001<br>C4591007<br>C4591010<br>C4591011<br>C4591012<br>C4591021 (former ACCESS/VAC4EU)<br>C4591038 (former C4591021 substudy)<br>C4591036 (former PHN)<br><br>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 |
|---|---|
| C4591001 | The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine.<br>An imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2. |
| C4591007 | To assess the safety, tolerability, immunogenicity, and efficacy of the BNT162b2 RNA-based COVID-19 vaccine candidate against COVID-19 in healthy paediatric subjects. |
| C4591009 | To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population (all ages), pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System. |
| C4591011 | To assess whether individuals (all ages) in the US DoD MHS experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine. |
| C4591012 | To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine including the bivalent Omicron modified vaccine, if feasible. |
| C4591010 | To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates. |

| Study | Purpose of the study |
|---|---|
| C4591015 | To assess safety and immunogenicity in pregnant women<br>In addition, exploratory objectives include:<br>(a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.<br>(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. |
| WI235284 | To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection. |
| WI255886 | To estimate the effectiveness of 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. |
| BNT162-01 Cohort 13 | To assess potentially protective immune responses in immunocompromised adults. |
| C4591024<br>(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 the bivalent Omicron modified vaccine in all authorized age groups, including individuals less than 12 years of age, if feasible.<br>Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination. |
| C4591038 (former C4591021 substudy) | To assess the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals (all ages) vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine. |
| C4591022 | To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age. |
| C4591036 (former Pediatric Heart Network study) | To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis including myocarditis after the bivalent Omicron modified vaccine, if feasible. |
| C4591030 (Co-administration study with seasonal influenza vaccine) | Safety and immunogenicity of COVID-19 mRNA vaccine and quadrivalent seasonal influenza vaccine when administered separately or concomitantly. |
| C4591031<br>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 |

| Study | Purpose of the study |
|---|---|
| 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 bivalent BNT162b2 RNA-based vaccine candidate(s) in healthy children. |

# PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

## Table of contents

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# ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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## Follow-up forms

Pfizer-BioNTech COVID-19 Vaccine VAED Data Capture Aid

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

**Instructions for use:**

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

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

**AER/Manufacturer Report #:** _____

**Suspect product:** _____

**Reported event term prompting special follow-up activities:** _____

**AE onset date (dd-Mmm-yyyy):** _____

**Patient Age (e.g., 65 years):** _____

**Patient Gender:** ☐ Male ☐ Female ☐ Not Stated

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

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

**Reporter Information**

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

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

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

## Follow-up Questions

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

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

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (and indicate if this is a new infection or a recurrence)*

*Details: (Please specify date of test and type of test – e.g., nasal swab reverse transcription–polymerase chain reaction (RT-PCR) test or nucleic acid amplification–based test (NAAT) or antigen test)*

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

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

*Details: (Please specify date of test, whether IgM /IgG or both and the titer if available)*

**3. Was/Is the patient hospitalized?**

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

*Details:*

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

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

*Details:*

**5. Is the patient still hospitalized?**

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

*Details:*

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

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

*Details: (Please specify date of test, whether IgM /IgG or both and the titer if available)*

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

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

*Details:*

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

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

*Details:*

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

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

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

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

*Details:*

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

*Details:*

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

*Details:*

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

*Details:*

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

*Details:*

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

*Details:*

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

*Details:*

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

*Details:*

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

*Details:*

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

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

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

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

*Details:*

**12. Patient's outcome with COVID-19:**

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

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

*Details:*

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

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

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

## Past Medical History Questions

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

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

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

*Details:*

**16. Is the patient a smoker/former smoker?**

☐ Current Smoker ☐ Former smoker ☐ No

*Details:*

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

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

*Details:*

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

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

*Details:*

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

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

*Details:*

## Revision History

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

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

**Instructions for use:**

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

**AER/Manufacturer Report #:** _____

**Suspect product:** _____

**Reported event term(s) prompting special follow-up activities:** _____

**AE onset date (dd-Mmm-yyyy):** _____

**Patient Age (e.g., 65 years):** _____

**Patient Gender:** ☐ Male ☐ Female ☐ Not Stated

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

**Reporter Information**

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

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

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

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

**3. FEVER**:

Measured temperature: Celsius: Fahrenheit:

Duration of fever (eg. 3 days):

**4. CLINICAL MANIFESTATION**

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

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

Gastrointestinal (abdominal pain, vomiting, diarrhea)

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

Shock or hypotension?

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

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

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

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: _____

**5. Are relevant lab values available?**

*Please indicate if the patient had any lab value abnormalities.*

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

**6.Were any relevant additional diagnostic evaluations performed?**

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

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

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

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

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

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

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

**Revision History**

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